Ellen Paap

Breast cancer screening effectiveness and the case-referent design: a well matched pair

Colofon

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a well matched pair

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Breast cancer screening effectiveness and the case-referent design: a well matched pair

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Voor papa,
je allerlaatste glimlach zei me dat het goed was zo.

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Chapter 1

Evaluating the effectiveness of the Dutch screening programme

In 1989, the national breast cancer service screening programme was implemented in the Netherlands. From then, women aged 50-69 (and from 1998 aged 50-75) have been invited to the screening programme every two years. In 2007, more than 1.1 million women received an invitation to participate in the screening programme.[1] *The objective of this programme was to reduce breast cancer mortality without adversely affecting the health status of those who participate.*[2]

The Dutch breast cancer service screening programme has now been running for 20 years. The current breast cancer mortality reduction can differ from results generated from the pilot programmes and randomised controlled trials on which the programme was implemented.[3-6] There have been many changes over time that may explain these differences. Skills and abilities can be different in the wider base of professionals carrying out service screening compared to the small group of researchers performing the mammography screening in the 1970s and 1980s. Furthermore, the anticipated breast cancer mortality reduction might be influenced by changes in baseline risk of breast cancer and differences in compliance to the programme. Improvements in mammographic and other techniques involved in screening, improvements in therapy and earlier diagnosis through increased breast cancer awareness, can also influence the reduction in breast cancer mortality.[7]

To guarantee a successful programme, all elements of the service screening programme itself, further diagnostic procedures and treatment of women for whom the screening examination yields abnormal results, have to be of high quality.[2] To ensure quality, monitoring and evaluation of the performance and impact indicators have to be embedded in the ongoing programme. After the start of the Dutch programme in 1989, quality assurance has been based on early indicators like the breast cancer detection rate and the proportion of screen-detected small invasive cancers (≤10mm).[2] In the randomised controlled trials of screening a decrease in the incidence of advanced breast cancer was approximately proportional to the decrease in breast cancer mortality and could thus act as an indicator of the effectiveness of a screening programme. However, this was not supported by trends in advanced breast cancer incidence in areas with widespread mammographic service screening, showing that advanced disease rate does not replace disease-specific mortality as the main end point.[8,9] Only 10 to 15 years following the start of screening, can reliable outcomes on breast cancer mortality be estimated.[10,11]

Breast cancer mortality can be evaluated using different methods: trend analysis, modelling, cohort and case-referent study designs.[12-16] All methods add relevant and valuable information to the evaluation of screening programmes. But only case-referent and cohort studies can be used for estimating the net benefit in risk reduction of women participating in the screening programme, as they link individual screening data with breast cancer death. Of these two methods, case-referent studies are recommended, because they are equally valid, more efficient and more cost-effective.[17,18]

However, the case-referent design is only an appropriate and valid method if specific methodological complexities are allowed for. The population from which the cases and referents are selected are women who received at least one invitation to the screening programme. Cases are defined as women who died from breast cancer. Referents are selected from the same population and have to be alive at time of death of the case.[19-22] The screening history is collected for all cases and referents. Screening participation of the cases is compared with that of the referents. If screening is effective, the participation of cases should be lower than the participation of referents. This results in an odds ratio below 1, for example 0.80, which indicates a 20% breast cancer mortality reduction due to screening. The protective element in screening is the treatment that follows the screening test, when the test is truly positive. Therefore, the odds ratio in a case-referent study measures the combination of early detection followed by appropriate treatment.[23]

A much discussed issue of the case-referent design is how to address the potential presence of self-selection bias. Women who accept the invitation to screening may have different baseline risks of breast cancer death compared to women who do not accept the invitation.[19,24] This potential difference in baseline risk can influence the estimate of breast cancer mortality reduction due to screening. For instance, if women who accept the invitation to screening have a lower breast cancer death risk, the reduction will be overestimated. Therefore, the odds ratio estimated from the case-referent study must be corrected for self-selection bias if present.

In 2006, the Dutch Cancer Society (KWF Kankerbestrijding[25]) approved the project: 'Impact of breast cancer service screening in the Netherlands: can case-referent studies reliably monitor and evaluate the effect on mortality?'. To address this research question, we have estimated the impact of screening mammography at both regional and national level, using individual data to directly link screening history with breast cancer death *(Chapters 3 and 4)*. In addition, we provide a correction factor for self-selection bias, calculated using the incidence-based mortality method based on data from the implementation phase of the Dutch screening programme (*Chapter 5*).[26] Recent case-referent studies in other countries have shown a wide range of breast cancer mortality reductions, from 25 to 50%. We have reviewed whether differences in the designs used may explain the differing mortality reductions *(Chapter 6)*. In the final chapter, the results and the future use of the case-referent design as a monitoring tool for the evaluation of the breast cancer screening programme in the Netherlands is discussed *(Chapter 7)*. As the impact of screening on mortality is dependent on the incidence in the population, we will start off this thesis by looking at trends in baseline morbidity and mortality of breast cancer over time *(Chapter 2)*.

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Large increase in a Dutch woman's lifetime risk of developing breast cancer.
E. Paap, M.J.M. Broeders, G. van Schoor, J.D.M. Otten, A.L.M. Verbeek.

Chapter 2

Lifetime risk of breast cancer in the screening era

Abstract

A large increase in the incidence of breast cancer has been observed in many countries over the last two decades. On the other hand, however, breast cancer mortality has decreased. The prominent burden of breast cancer in the female population induces a lot of discussion about incidence and mortality rates, whereas lifetime risks are less mentioned. This study provides information on the changes in risks for Dutch women with regards to being diagnosed with breast cancer (both invasive and in situ) or dying from this disease during the screening era.

We used the life table method to calculate lifetime risks for the period 1989–2003. The lifetime risk for developing breast cancer increased from 1 in 10 in 1989 to 1 in 7 in 2003; the risk of dying from breast cancer decreased respectively from 1 in 22 to 1 in 26. The increasing incidence is alarming but has to be seen in perspective; the decreasing mortality is promising and shows that, at most, one third of the breast cancer cases are fatal.

Introduction

The prominent burden of breast cancer in the female population has resulted in a great deal of interest in all topics concerned with breast cancer. Since the implementation of service screening in many countries, the changes in both the incidence of and mortality rates from breast cancer have been widely discussed in the literature.[1,2]

The increased incidence and decreased mortality in many European countries is demonstrated in a recent study by Héry and colleagues which reported on changes in breast cancer incidence and mortality in middle-aged and elderly women in 28 countries.[3] In the Netherlands nearly 13,000 women are diagnosed with an invasive or in situ breast carcinoma each year.[4]

Although rates have regularly been reported in the literature, in the popular press, lifetime risk is a widely cited statistic used for communicating risks to the general population.[5] The lifetime risk represents the average risk at birth that a woman will develop breast cancer or die from breast cancer during her lifetime.[6] We wanted to know the effect of the changes in rates on the individual lifetime risk. This study provides information on these changes in lifetime risk over the past two decades.

Patients and methods

Data

To calculate the lifetime risk we have used the life table method. Female breast cancer incidence, mortality and population data were obtained from the Netherlands Cancer Registry (NCR) and Statistics Netherlands for the years 1989–2003.[4,7] We used the absolute numbers of newly diagnosed breast cancer patients (invasive and carcinoma in situ) and the absolute numbers of breast cancer deaths of age groups of five years: 0–4, 5–9, . . ., 90–94 and 95+. The 95+ age group included women aged 95 and older.

Life table method

In 1956, Goldberg and colleagues pioneered the life table method, which calculates the lifetime risks by means of a fictitious cohort of women from birth on the basis of life expectancy and the current incidence or mortality.[8] This estimate of the lifetime risk can be computed if data on breast cancer morbidity, mortality and life expectancy tables are available.[9] For determining the life table risk for breast cancer we used the method of Fay and colleagues with DevCan software, version 6.1.0, from the US National Cancer Institute.[10-12]

We estimated the change in risk of developing or dying from breast cancer for two different age spans, namely the lifetime risk and the risk until age 75.

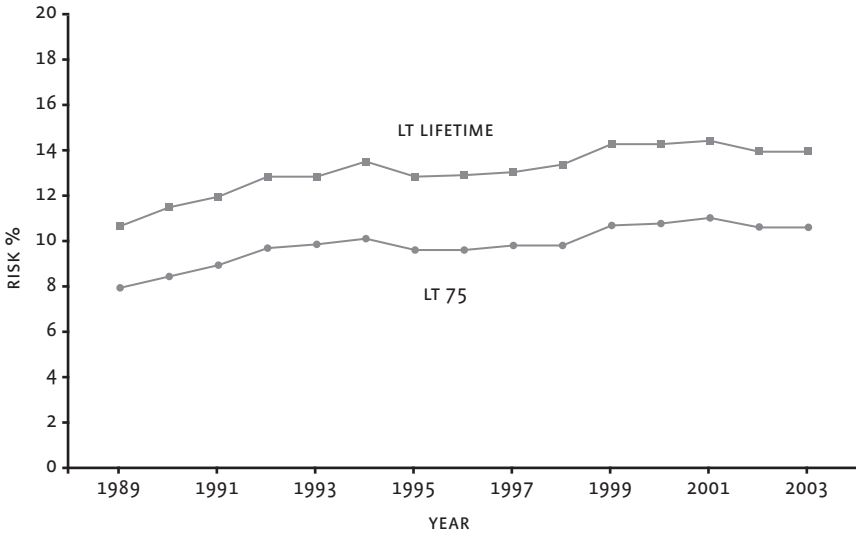

FIGURE 2.1 Change in risk of developing breast cancer (invasive and in situ) for the period 1989 - 2003 for the age groups up to 75 and for lifetime

Results

The results in *Figure 2.1* show how the risk of developing breast cancer has changed over time. Both the lifetime risk and the risk up to 75 years of age show a considerable increase in risk over the last two decades. According to the life table method, 10.5% of all women born in 1989 will develop breast cancer, while for women born in 2003 this risk increases to 13.6%. The risk of developing breast cancer before the age of 75 increases from 7.8% in 1989 to 10.4% in 2003.

In *Table 2.1*, we converted the percentages to an individual risk. Using data from 1989, 1 in 10 women will develop breast cancer. By 2003, this has increased to 1 in 7 women. The risk of developing breast cancer before the age of 75 is 1 in 10 in 2003.

Figure 2.2 and *Table 2.1* illustrate the change in risk of breast cancer death during the screening era. The lifetime risk of dying from breast cancer declined from 4.6% (1 in 22) in 1989 to 3.9% (1 in 26) in 2003. Up to the age of 75, the risk decreased from 2.6% in 1989 to 2.2% in 2003.

TABLE 2.1 Individual risks of developing breast cancer and dying from breast cancer for a woman born in 1989 and for a woman born in 2003

	Risk of developing breast cancer		Risk of dying from breast cancer	
	1989	2003	1989	2003
Lifetime risk	10.5% 1 in 10	13.6% 1 in 7	4.6% 1 in 22	3.9% 1 in 26
Risk before the age of 75	7.8% 1 in 13	10.4% 1 in 10	2.6% 1 in 38	2.2% 1 in 45

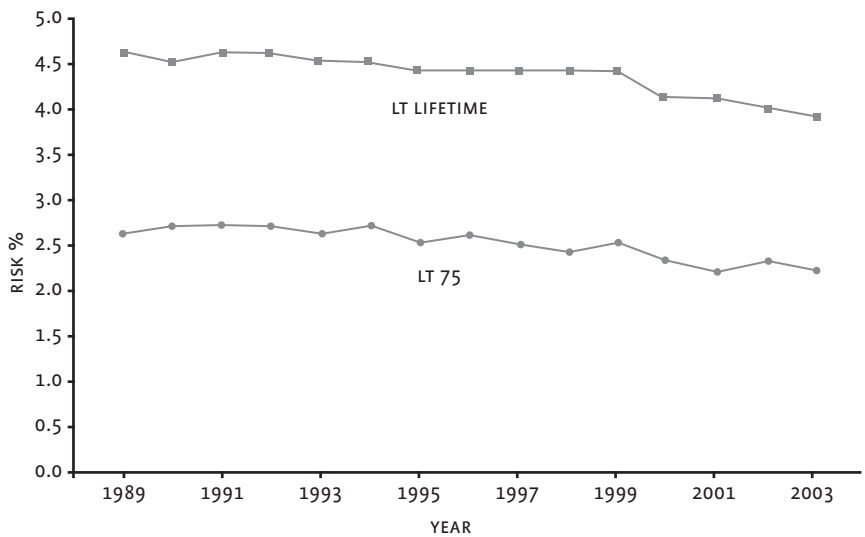

FIGURE 2.2 Risks of dying from breast cancer for the age groups up to 75 and for lifetime during the screening era

Discussion

The results of our study show a large increase in the female lifetime risk of developing breast cancer over the last two decades. Although this increase is obvious, the reasons for it are still debated. One factor that can be associated with the increase is that women live longer and die less often from other causes.[5] A second possible explanation is the change of exposure to risk factors over the past decades – for example, change in risk factors related to pregnancy, obesity and mammographic density.[13,14] Soerjomataram and colleagues observed a strong correlation between the overall excess incidence of breast cancer and the average age of the mother at first birth.[15] Besides a high average of mean age at first birth, populations in countries with a high breast cancer risk tend to have a clustering of other risk factors, for example, younger age at menarche and a higher body mass index.[16] Furthermore, the increase in lifetime risk is often mentioned as an effect of the introduction of service screening, which started in the Netherlands in 1989.[17] For example, overdiagnosis due to service screening has been noted as a possible reason.[18,19] It is, however, unlikely that the increase in incidence is entirely attributed to screening.[15] Even if this debate about the reasons for the increased incidence is solved, the question to what extent breast cancer could be prevented will remain.

In Europe, breast cancer incidence shows an increasing trend in many countries.[3,17] Ferlay and colleagues have demonstrated that, in 2006, the Netherlands, after Belgium and Ireland, had the highest incidence rate in Europe.[2] This high incidence rate reflects a high lifetime risk for breast cancer compared to other European countries.

Some remarks on the level of the current lifetime risk have to be made. The risk estimate is based on the entire female population and is therefore an average. Individual lifetime risks depend on the presence or absence of risk factors in the individual woman. In addition, surviving to an increased age results in a lower lifetime risk in the remainder of a woman's life.[5,20,21] According to the Dutch Cancer Society the current lifetime risk of developing an invasive breast cancer for a Dutch woman is 1 in 8. The remaining lifetime risk for a woman aged 50 is 1 in 9 and for a woman aged 60, 1 in 12.[22] The risk of developing breast cancer before the age of 75 (1 in 10) is considerably lower than the lifetime risk, because breast cancer incidence increases with age.

Besides an increased chance of developing breast cancer, the results demonstrate a decrease in risk of dying from breast cancer. The risk of dying before the age of 75 is even lower. The low mortality risk compared to the high incidence risk can be credited to diagnosis of breast cancer in an early stage and to improved therapy.[1]

The implementation of the breast cancer service screening in the Netherlands has introduced, among other things, an increase of carcinoma in situ over the last two decades.[23] In calculating lifetime risks of developing breast cancer, we included patients with a carcinoma in situ because these women are treated in the same way as women

with a small invasive carcinoma.[23,24] It should be pointed out that in using the numbers from the Netherlands Cancer Registry, women who develop a second breast cancer with a different morphology are counted twice. Inclusion of the carcinoma in situ in our calculations will overestimate the risk of developing breast cancer because some of these women develop an invasive carcinoma later in life. A rough estimate of this overestimation is that the risk of developing breast cancer decreases by 0.2%, which would lead to an individual life table risk of 1 in 7.5.

In conclusion, the breast cancer incidence has increased to a high level and currently 1 in 7 Dutch women will develop breast cancer sometime during their life. Although the incidence has increased, the mortality has decreased during the last two decades and at the moment the risk of dying is 1 in 26.

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A remarkable reduction of breast cancer deaths in screened versus unscreened women:
a case-referent study.
E. Paap, R. Holland, G.J. den Heeten, G. van Schoor, A.A.M. Botterweck,
A.L.M. Verbeek, M.J.M. Broeders.

Chapter 3

Estimating effectiveness in Mid and South Limburg

Abstract

Objective – *We designed a case-referent study to investigate the effect of mammographic screening at the individual level, looking at the association of breast cancer death with screening history.*

Methods – *The study population included all women aged 50–75 in the province of Limburg, the Netherlands who had been invited to the screening program from 1989 to 2006. From this population, 118 cases originated who died of breast cancer in 2004 or 2005. The screening history of these cases was collected and compared with a sample of the invited population. The breast cancer death rate in the screened relative to the unscreened women was estimated as the odds ratio (OR). This OR was adjusted for self-selection bias, the difference in baseline risk for breast cancer death between screened and unscreened women.*

Results – *Analysis of the data showed a breast cancer mortality reduction of 70% in the screened versus the unscreened women (OR = 0.30, 95% CI 0.14–0.63). The magnitude of self-selection was estimated specifically for Limburg. After correction for self-selection bias, the effect of screening increased to 76% (OR = 0.24, 95% CI 0.10–0.58).*

Conclusion – *Screening resulted in a remarkable reduction in breast cancer mortality. Contrary to findings in other countries, adjustment for self-selection in Limburg had no influence on the impact of screening. Thanks to a well-organized centralized screening program, similar results are expected in other regions of the Netherlands.*

Introduction

Several randomized controlled trials conducted in the 1970s and 80s have shown a breast cancer mortality reduction of 25–30% in those offered mammographic screening.[1] As a consequence, many countries initiated a national or regional service screening program. In the Netherlands, a population-based program was set up in 1989 with a centralized organization, including centralized technical and medical quality control, and audit.[2]

Since the introduction of service screening in the Netherlands, there has been a large decrease in breast cancer mortality. A trend study by Otten et al. provided support for a time relation between the implementation of screening and its effect on breast cancer mortality.[3] This mortality reduction was preceded by a significant decrease in advanced disease from 1995 onwards.[4] Although trend studies suggest that screening affects breast cancer mortality, they cannot show a direct link between screening performance and breast cancer death. Other factors like improvements in therapy could also be (partially) responsible for the decrease in mortality.[5] Therefore, individual data on screening history, diagnosis and breast cancer death should be analysed.

In the Dutch screening program, women aged 50–75 are invited for biennial mammography screening. During the performance of our study, one of the regions which organized breast cancer screening was the Comprehensive Cancer Centre Limburg (IKL). The IKL covers a large part of the province of Limburg with a female population of 450 000 representing 6% of the Dutch female population.

In this region, no study has yet estimated the relation of breast cancer death with screening history at an individual level. An efficient method for evaluating this relation is the case-referent study.[6] This design requires consideration of self-selection bias since women who accept the invitation to screening may have a different baseline risk for breast cancer death a priori than women who do not accept the invitation.[7]

The aim of this study was to evaluate the association between service screening and breast cancer mortality in the province of Limburg using a case-referent design. We were able to adjust this effect for self-selection based on differences in baseline risks of breast cancer death by screening status in the female population of Limburg.

Methods

Study population

The study population included women aged 50–75 who received at least one invitation to the service screening program in the IKL-region. During our study, the IKL included both a cancer and a screening registry. The cancer registry collects data on all patients with breast cancer in the covered region. The screening registry holds individual data on invitation and participation for all women in the target population of the service screening program in the IKL-region.

We applied a case-referent design to evaluate the effect of current mammographic screening on breast cancer mortality. Cases originated from the study population and were defined as women who died from breast cancer in 2004 or 2005. The cause of death as reported in death certificates was obtained through linkage with Statistics Netherlands. Data collection for cases included date of death, date of diagnosis, date of birth and the complete screening history. For each case, one referent was sampled from the study population. The referent was matched for year of birth and area of residence. She had to be free of breast cancer at the moment she received the invitation to screening (index invitation) and had to be alive at time of death of the case. The complete screening history of each referent was also included in the database. The case and her matched referent formed a case-referent set.

Definition of exposure to screening

The screening history of cases and referents included their dates of invitation and the dates of their screening tests if they participated. Screening participation can only influence breast cancer death if the screening examination is performed in the period when the cancer is potentially detectable on the mammogram — in the detectable preclinical period (DPCP). Therefore, for each case, we set the opportunity to exposure to screening to be the most recent invitation date preceding the diagnosis, the index invitation.[8] In the case-referent set, the referent was also assigned an index invitation from the same screening round from which the index invitation of the case was selected. Both the case and the referent are classified as screened if they participated in the screening examination following their index invitation. For screen-detected cases, this was the screening examination at which the breast cancer was detected.

The exact duration of the DPCP varies for cases, but will probably not exceed four to six years, based on estimates of lead time for breast cancer diagnosis.[8,9] Including only the index invitation to classify exposure to screening could lead to underestimation of the effect of screening.9 In an additional analysis, we therefore expanded the opportunity for exposure to screening to the invitation preceding the index invitation.

Statistical analysis

The case-referent comparison relates screening participation at the index invitation to breast cancer death. The breast cancer death rate in the screened versus the unscreened women was assessed and represented as an odds ratio (OR). This was achieved by calculating the Mantel–Haenszel odds ratio and its 95% confidence interval by means of conditional logistic regression, taking into account, the matching for year of birth and area of residence. Matching the referent to the case leads to four possibilities for a case-referent set: the case and referent are both screened; the case is screened but the referent not; the case is not screened but the referent is; both the case and referent are not screened. The OR for a matched case-referent study only includes the discordant

case-referent sets. The OR is calculated as the number of sets where the case is screened and the referent is not, divided by the number of sets where the case is not screened and the referent is.[10]

Self-selection bias

In the evaluation of breast cancer screening, much attention has been paid to self-selection bias.[11] Participation in screening is based on a voluntary decision. Therefore, the baseline risk for breast cancer death could be different beforehand in the screened women compared to the unscreened women, for example due to differences in ethnicity, history of relatives with breast cancer, or socioeconomic circumstances.[12-14] To correct for potential self-selection bias, we calculated a correction factor specifically for the IKL-region using the incidence-based mortality (IBM) method of Paci et al.[15] To this end, we used data of women eligible for invitation to screening during the implementation period of the screening program (1990–1995). For this period, we calculated the IBM rate for women not yet invited to the screening program and for women invited, but not screened. The numerator of the IBM rates included breast cancer deaths of women diagnosed with breast cancer in the years 1990–1995. In total, 188 uninvited and 34 not screened breast cancer deaths were identified. The person years in the denominator were calculated with data on the number of invited, number of screened and the total female population in the years 1990–1995. The correction factor is the relative risk of breast cancer death for not screened versus not yet invited women.[16] For the IKL-region, the correction factor was 0.84 (95% CI: 0.58–1.21), indicating a lower baseline risk in women who do not attend screening. This factor was used in a formula developed by Duffy et al. to correct the estimated odds ratio for self-selection bias.[16,17]

Results

In total, 118 cases and 118 referents were selected in the IKL-region. The mean age at index invitation for the cases was 61.7 (range 49.4–75.3). *Table 3.1* shows the number of case-referent sets according to their participation in screening following the index invitation. The breast cancer mortality reduction was 70% in screened women compared to unscreened women (OR = 0.30, 95% CI 0.14–0.63). As mentioned in the methods section, this odds ratio has to be corrected for self-selection bias. *Table 3.2* shows the formula of Duffy et al.: $OR_{adjusted} = p\ \psi\ D_r/(1-(1-p)D_r)$, where p is the attendance rate for service screening in Limburg (82%), ψ the uncorrected odds ratio (0.30) and D_r the correction factor for self-selection bias (relative risk of breast cancer death; 0.84). This formula results in a mortality reduction of 76% (OR = 0.24, 95% CI 0.10–0.58).[16]

If we expanded the opportunity for exposure to screening to the invitation preceding the index invitation in the analysis, the achieved mortality reduction changed slightly from 70 to 73% (OR = 0.27, 95% CI: 0.12–0.62).

TABLE 3.1 Case-referent sets, their participation in the screening examination following their index invitation and the calculated odds ratios

	Number of case-referent sets
Case and referent both screened	69
Case screened, referent unscreened	9
Case unscreened, referent screened	30
Case and referent both unscreened	10
Total of case-referent sets	118
Odds Ratio (95% CI)	0.30 (0.14-0.63)
Odds Ratio adjusted for self-selection (95% CI)	0.24 (0.10-0.58)

TABLE 3.2 Effect of screening on breast cancer mortality: odds ratio adjusted for self-selection bias

Formula of Duffy[16]	$p\,\psi\,D_r/(1-(1-p)D_r)$
Where	
ψ - unadjusted odds ratio (95% CI)	0.30 (0.14-0.63)
p - attendance rate of screening in Limburg	0.82
D_r - correction factor for self-selection in IKL-region (95% CI)	0.84 (0.58-1.21)
	0.82 x 0.30 x 0.84 / (1-0.18 x 0.84)
OR adjusted for self-selection bias (95% CI)	0.24 (0.10-0.58)

Discussion

In this study, we report two important findings, namely a remarkable breast cancer mortality reduction of 70% in screened women compared to unscreened women, and continuation of this effect of screening after adjustment for self-selection bias. In other countries, estimates of the impact of service screening on breast cancer mortality showed reductions of 34–65%, however, with no adjustment for self-selection bias.[18] In view of these findings, our results indicate a higher impact of mammographic service screening on breast cancer mortality in the IKL-region.

A number of reasons for this remarkable effect of screening in the Netherlands can be put forward. It could result from the high-quality screening in a centrally organized program.[2] A second reason could be improvements due to progression in quality assurance and advancements in mammographic techniques. In addition, improvements in therapy

could also have resulted in a larger combined effect of screening and therapy. Breast cancer screening can only reduce mortality if early diagnosis is followed by appropriate (early) treatment. For example, adjuvant systemic therapy was introduced and used on a large scale before the implementation of the screening program, which probably contributed considerably to the breast cancer mortality reduction.[5]

The influence of self-selection in the province of Limburg was minor. After adjustment for self-selection, the mortality reduction in screened women changed from 70 to 76% compared to unscreened women. This is contrary to results obtained in other countries, where the impact of screening reduced after correction for self-selection (breast cancer mortality reductions of 34–65% before and 25–50% after adjustment for self-selection).[18]

In our study, we calculated a correction factor for self-selection specifically for the province of Limburg, indicating a lower baseline mortality risk in women not attending screening. Recent case-control studies used a correction factor for self-selection based on data from randomized controlled trials in Sweden and Canada.[7,16,17] This correction factor was 1.36, indicating a higher baseline mortality risk in the unscreened women. Two other case-control studies also calculated their own correction factor, of 1.11 and 1.17.[19,20] These differences show that self-selection can differ in magnitude and direction between countries or regions. This demonstrates the importance of using a regional or national correction factor for self-selection, where possible. Factors which could be associated with lower breast cancer risk factors in unscreened women in Limburg are unclear, but could for example be due to a lower number of relatives with a history of breast cancer, to differences in socio-economic status, to ethnicity, or to screening outside the screening program in unscreened women.[13,14,21-24] Further research should explore the background of the lower baseline risk for breast cancer death in unscreened women in the IKL-region.

The primary analysis of the association included participation of the case and referent following the index invitation. The additional analysis including the invitation prior to the index invitation, resulted in a small change in the mortality reduction from 70 to 73%. This indicates that the underestimation of the DPCP is of minor impact in our study.

Because the region of the IKL is small, the number of cases and referents is quite low (118 case-referent sets). Despite this low number, the confidence interval has an acceptable range: from 0.14 to 0.63. This is also true for the calculation of the correction factor for self-selection. At this moment, more regions in the Netherlands are being included in a multi-region study to support our findings in the IKL-region. Thanks to the well-organized centralized and medically audited screening program, we expect similar results in these regions.[2]

In conclusion, the service screening in Limburg resulted in a remarkable reduction of breast cancer mortality. This study includes a correction factor calculated specifically for this region using the incidence-based mortality method. Contrary to other countries, adjustment for self-selection had no influence on the impact of screening. Although disadvantages of screening exist, for example overdiagnosis[25,26], the positive results from

our study show a clear breast cancer mortality reduction, the ultimate benefit of breast cancer screening.

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Chapter 4

Breast cancer screening effectiveness in the Netherlands

Abstract

Background – *Mammographic screening programmes have been implemented in many Western countries to reduce the burden of breast cancer mortality, however the benefits are still subject to debate. We investigated the benefit of the Dutch population-based screening programme by analysing the reduction in breast cancer mortality using individual invitee data.*

Methods – *In a large multi-region study, we identified all breast cancer deaths in 2004 and 2005 in women diagnosed with breast cancer in the age group (50-75y) invited for screening. Women who died of breast cancer (cases) were individually matched for year of birth and area of residence to referents from the population invited to screening. Individual screening histories were used to calculate the odds ratio (OR), which represents the breast cancer death rate in screened versus unscreened women. The OR was adjusted for self-selection bias using regional correction factors for the difference in baseline risk for breast cancer death between screened and unscreened women.*

Results – *A total of 1233 cases and 2090 referents were included in this study. We found a 58% reduction in breast cancer mortality in screened versus unscreened women (OR = 0.42 , 95% CI 0.33-0.53).*

Conclusion – *Our study shows that the Dutch breast cancer screening programme leads to a substantial reduction in breast cancer mortality, demonstrating the effectiveness of this programme. Communication of these results to the women invited to the screening programme could help them make a balanced decision about the value of attending screening.*

Introduction

Screening mammography is effective in reducing breast cancer mortality for women aged 50-69, as demonstrated in breast cancer screening trials in the 1970s and 1980s.[1] On the basis of these trial results, mammographic screening programmes have been implemented in many Western countries in the 1990s to reduce the burden of breast cancer mortality. Currently, the benefits are still subject to debate. It is questioned whether the mortality reduction is large enough to justify the harms of screening.[2,3]

A few recent studies that compare invited with not-invited areas within the same countries have not found a (large) effect of current mammography screening programmes, whilst others did.[4-8] This type of analysis potentially underestimates the effect of screening in subjects actually screened, due both to noncompliance in the invited areas and contamination ('ad hoc' screening) in the not-invited areas.[9] To communicate the level of protection that an individual woman can expect if she complies with screening, it is more relevant to compare screened with not screened women.[10,11] However, this comparison has been criticized because self-selection bias could distort the relation between screening mammography and breast cancer mortality.

To assess the effect of screening on breast cancer mortality reliably, it is necessary to directly link a woman's cause of death and her screening history.[12] In this study, we estimated the benefit of the current Dutch population-based screening programme by comparing breast cancer mortality in screened versus unscreened women. To adjust for self-selection bias, we provided regional correction factors for potential self-selection bias estimated from the implementation phase of the Dutch programme.[13]

Patients and methods

Dutch breast cancer screening programme

A population-based breast cancer service screening programme was gradually implemented in the Netherlands from 1989 onwards. Dutch screening policy recommends bilateral mammography for all women aged between 50 and 69, with a biennial screening interval. Coverage of the target population, that is, the percentage of eligible women annually invited, increased from 11% in 1990, to 69% in 1993, and to full population capacity in 1996. In 1997, the upper age limit was extended to 75 years with full coverage in 2001. In 2007, more than 1.1 million women received an invitation to participate in the screening programme, and over 900,000 women were screened (mean overall attendance rate of 82.4%).[14]

Between 1989 and 2009 the organization of the screening programme was executed by nine regional screening organisations. Of these, five have been included in our study: Stichting Kankerpreventie en -screening Limburg (SKsL), Stichting Kankerpreventie IKA

Source: www.bevolkingsonderzoekborstkanker.nl (screening regions between 1989 and 2009)

FIGURE 4.1 Five out of nine screening regions included in our case-referent study: SKsL, SKP IKA, BBNN, SVOKON and SBBZWN

(SKP IKA), Stichting Bevolkingsonderzoek Noord-Nederland (BBNN), Stichting Vroege Opsporing Kanker Oost-Nederland (SVOKON) and Stichting Bevolkingsonderzoek Borstkanker Zuidwest Nederland (SBBZWN). Those screening regions cover more than half of the target population for screening in the Netherlands and were selected based on the geographical distribution of rural and urban areas (*Figure 4.1*) and early and late implementation of the screening programme. The screening organisations have screening registries which hold individual data on invitation, participation and screening outcome for all women in the target population of the service screening programme.

Study population

Our study population included all women aged 50–75 years who received at least one invitation to the service screening programme in the five participating screening regions. Cases for the case-referent study originated from the study population and were defined as women who died from breast cancer in 2004 or 2005. All members of the study population were linked with the Netherlands Cancer Registry to identify breast cancer patients who died in 2004 or 2005. The cause of death is not known in the Cancer Registry. Therefore, the breast cancer patients who died in 2004 or 2005 were then linked with the of Cause of Death Registry of Statistics Netherlands to obtain cause of death as reported in death certificates.

Data collection for cases included date of death, date of diagnosis, date of birth and the complete screening history. Cases were only included if their date of diagnosis was after the date of their first invitation. For each case, referents were sampled from the study population. For the first two screening organisations included in this study, SKsL and BBNN, one referent was matched to each case, due to financial constraints. In the other three organisations it was possible to include two referents for each case. The referents were matched for year of birth and area of residence. They had to be free of breast cancer at the moment they received the invitation to screening and had to be alive at the time of death of the case. The complete screening history of each referent was also included in the database. The case and the matched referent(s) formed a case-referent set.

Screening history

Screening participation can only influence breast cancer death if the screening examination is performed in the period when the breast cancer is potentially detectable on the mammogram before symptoms appear.[15] The exact duration of this period is unknown for the individual patient, but will most probably be within a 4-year period before clinical breast cancer diagnosis, based on estimates of lead time for breast cancer diagnosis.[15,16]

For this reason, we looked at screening participation for each case with a maximum of two screening rounds preceding the diagnosis. The most recent invitation before diagnosis is termed the index invitation. In the case-referent set, the referent was also assigned an index invitation from the same screening round from which the index invitation of the case was selected. Both the case and the referent are classified as screened if they participated in the screening examination following their index invitation and/or the invitation in the screening round before the index invitation. For screen-detected cases, this was the screening examination at which the breast cancer was detected.

Self-selection bias

Self-selection is present when women who decide to participate in screening have a different baseline risk of breast cancer mortality to those who decide not to participate. This could be due, for example, to differences in ethnicity, history of relatives with breast cancer, or socioeconomic circumstances.[17-19] To correct for potential self-selection bias, we calculated a correction factor for each region using the incidence-based mortality (IBM) method.[20] Data was gathered from women eligible for invitation to screening during the implementation period of the screening programme (1990–1995). We calculated the IBM rate for women not invited to the screening programme and for those invited, but not screened. The numerator of the IBM rates included breast cancer deaths of women diagnosed with breast cancer in the years 1990–1995: in total, 2631 uninvited and 345 not screened breast cancer deaths were identified. The person years in the denominator were calculated using data on the number of invited, number of screened and the total

TABLE 4.1 Background information of the included regions, and odds ratios with and without correction for self-selection bias for the Netherlands and the five participating screening regions separately

	Number of invitations (2004 and 2005)	Attendance rate (%) (2004 and 2005)	Cases/referents (N)	Odds ratio previous and index invitation (95%-CI)	Correction factor for self-selection (95%-CI)	Odds ratio adjusted for self-selection bias (95%-CI)
Overall	1.256,688	80.8	1233/2090	0.48 (0.40-0.58)		0.42 (0.33-0.53)[a]
BBNN	299,256	84.6	258/258	0.67 (0.42-1.08)	0.64 (0.46-0.90)	0.40 (0.22-0.74)
SKP IKA	356,973	78.8	343/686	0.52 (0.38-0.73)	0.77 (0.63-0.93)	0.38 (0.25-0.57)
SKsL	133,816	83.8	118/118	0.27 (0.12-0.62)	0.92 (0.65-1.30)	0.24 (0.10-0.62)
SBBZWN	296,051	77.6	330/660	0.44 (0.32-0.60)	1.08 (0.82-1.43)	0.49 (0.30-0.78)
SVOKON	170,592	81.9	184/368	0.46 (0.30-0.72)	1.08 (0.85-1.37)	0.51 (0.30-0.87)

[a] *Pooled odds ratio based on the five regional adjusted odds ratios*

TABLE 4.2 Example of adjustment of OR for self-selection bias in the region of BBNN

Formula of Duffy[21]	$p\,\psi\,D_r/(1-(1-p)D_r)$
Where	
ψ - unadjusted odds ratio (95% CI)	0.67 (0.42-1.08)
p - attendance rate of screening	0.85
D_r - correction factor for self-selection (95% CI)	0.64 (0.46-0.90)
	0.85 x 0.67 x 0.64 / (1 - 0.15 x 0.64)
OR adjusted for self-selection bias (95%CI)	0.40 (0.22-0.74)

female population in the same period. The correction factor is the rate ratio of breast cancer death for not screened versus not yet invited women.[21] Ultimately, the correction factor can be used to adjust a difference in baseline risk for not screened versus screened women. A detailed description of the estimation of the regional correction factors can be found in Paap et al.[13]

Statistical analysis

To estimate the effect of screening on breast cancer mortality, we used conditional logistic regression to calculate odds ratios (OR) and the 95% confidence interval, taking into account the matching for year of birth and area of residence. The OR indicates the breast cancer death rate in screened versus unscreened women. Sub-analyses were conducted for each of the five regions separately. To adjust for self-selection bias we first adjusted the regional ORs with the formula developed by Duffy et al., because heterogeneity between the regional correction factors was shown.[13,21] After that, we pooled the regional corrected ORs to provide a national estimate for breast cancer mortality reduction due to screening, using the inverse variance method.[22]

Results

A total of 1233 cases and 2090 referents were included in this study. Of the cases, 49% were aged 49-59 at the index invitation, 38% aged 60-69 and 13% aged 70-75 years. Because cases and referents were matched for year of birth, the percentages for the different age groups were the same for the referents. The mean age at diagnosis for the cases was 61.9 (standard deviation 7.3) years. Most cases were diagnosed in the years 2001-2005 (53%) compared to 36% in the years 1996-2000 and 11% in the years 1990-1995.

Without correction for self-selection bias, the overall OR showed a breast cancer mortality reduction of 52% (OR = 0.48, 95% CI 0.40-0.58) for screened women compared to not screened women (*Table 4.1*). The regional ORs, without correction for self-selection, ranged from 33% (OR = 0.67, 95% CI 0.42-1.08) mortality reduction in the BBNN region to 73% (OR = 0.27, 95% CI 0.12-0.62) in the SKsL region.

In the SBBZWN, SKsL and SVOKON regions the correction factor was around one, indicating no presence of self-selection in those regions. The correction factor for BBNN was 0.64 (95% CI: 0.46-0.90) and for SKP IKA 0.77 (95% CI: 0.63–0.93), both indicating a lower baseline risk in women who do not attend screening versus screened women (*Table 4.1*). An example of the correction for self-selection is given in *Table 4.2* for the region of BBNN.

The pooling of the regional adjusted ORs resulted in a breast cancer mortality reduction of 58% (OR = 0.42, 95% CI 0.33-0.53, *Table 4.1*).

Discussion

Our results demonstrate a breast cancer mortality reduction of 58% (OR = 0.42, 95% CI 0.33-0.53) due to breast cancer screening. The protective element in screening is the treatment that follows the screening test, when the test is truly positive. Therefore, the odds ratio in a case-referent study measures the combination of early detection followed by appropriate treatment.[23] A special feature of this study is that we used regional-specific correction factors to adjust for self-selection bias, which showed only a minor influence on the overall effect estimate in the Netherlands. Only a limited number of studies have used country or region-specific estimates for self-selection.[7,8,24,25]

In this large multi-region study we have estimated the current benefit of screening. An optimal screening effect is not achieved in the first years of screening because prevalent screen-detected cases benefit less.[26,27] Prevalent screen-detected cases are women diagnosed in the first round of screening or in a woman's first test at a subsequent round.[20] Therefore, they dominate the first years of the implementation of screening programmes. By including cases who died in 2004 or 2005, the proportion of women diagnosed in the first years after the start of a screening programme is small and results in an estimate of the current benefit of the screening programme.

In other countries, 25 to 50% breast cancer mortality reductions have been found when comparing screened women to unscreened women.[28,29] In the Netherlands, regional estimates of the impact of screening have consistently demonstrated the effectiveness of the Dutch screening programme in those regions.[30-32] In line with these regional studies, this nationwide study confirms that the centrally organised Dutch population-based screening programme is highly effective in reducing breast cancer mortality.

Our result is at least consistent with the results from the breast cancer screening trials from the 1970s and 1980s, after adjusting for contamination and non-compliance.[10] The randomised controlled trials showed mortality reductions of 20-30% based on intention to treat analyses, thus comparing the breast cancer mortality in invited women with not-invited women. Translation of our effect in those actually screened to an intention to treat analysis would result in a reduction equivalent to 48% (95% CI 39%-56%).[21]

A major criticism of observational studies is that women who attend screening might differ from those who do not, so that any observed effect might not be causal. When nationwide screening is offered to all women in the target group, a well-defined control group is no longer available. In this situation, the only period from which a control group can be created is directly before the start of the implementation of a screening programme or during the implementation of the screening programme, when part of the target group is still not-invited.

During the implementation phase of the Dutch screening programme, the female population in the targeted age group shifted from an uninvited population to an invited population, providing us with contemporaneous groups of not invited and invited but

not screened women. Therefore, we adjusted for self-selection using correction factors based on breast cancer patients diagnosed in the period 1990 to 1995. Correction for self-selection bias of an estimated odds ratio for recent years would assume that the differential between the non-screened and not-invited women does not change over time. This assumption is inevitable, but is supported by the high and stable attendance rate in the Netherlands, which suggests that the non-screened women have not changed over time.

Age is strongly related with both the occurrence of breast cancer death and screening participation. In this study we matched for age, thereby correcting for the influence of this confounder. Other than age there is no background information available on other possible risk factors for breast cancer. Other risk factors like mammographic density, socioeconomic status and obesity could theoretically distort the relation between breast cancer screening and breast cancer mortality, however we demonstrated that these factors only play a minor role in the evaluation of screening programmes.[33] Therefore, we assume that any other confounding factors will not change the estimated benefit of the screening programme largely.

In conclusion, the current Dutch breast cancer screening programme has achieved a substantial reduction in breast cancer mortality. Because the benefits found in this study are based on screened versus unscreened women, communicating these results to the invited population could help women make a balanced decision about the value of attending screening.

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Minor influence of self-selection bias on the effectiveness of breast cancer screening in case-control studies in the Netherlands.
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Chapter 5

Addressing self-selection bias

Abstract

Background – *Self-selection bias is considered to be a problem when evaluating the effectiveness of breast cancer service screening in case-control studies.*

Objective – Using the incidence-based mortality method (IBM), a correction factor for the potential influence of self-selection can be derived from a group of non-screened women and a group of not-invited women.

Methods – *Breast cancer patients, diagnosed in 1990-1995 between the ages of 50 to 70, were selected from the Netherlands Cancer Registry and five screening regions in the Netherlands. Person-years were calculated for non-screened and not-invited women by using population data available on the number of women invited, the number of women screened and the total population. Incidence-based breast cancer mortality rates according to screening status were calculated for the five screening regions.*

Results – *Between 1990-1995, 15 541 patients were diagnosed with breast cancer. An analysis of ten year follow-up after diagnosis resulted in 3903 breast cancer deaths, of which 2631 were not-invited and 345 were non-screened. Poisson regression analysis showed heterogeneity between the regions with a range of IBM ratios from 0.64 (95% CI 0.46-0.90) to 1.08 (95% CI 0.82-1.43).*

Conclusions – *Heterogeneity between the regions stresses the importance of a country- and/or region-specific estimate of self-selection. Adjusting for self-selection bias in the regional case-control studies would not change the breast cancer mortality reduction in three regions and would result in an even larger effect in two regions. Looking at the range of IBM ratios the overall influence of self-selection in the Netherlands is minor.*

Introduction

The case-control study is regularly used as a tool for the evaluation of the effect of screening on breast cancer mortality.[1-8] A problem associated with case-control studies is the possible influence of self-selection bias on the magnitude of the effect of screening. Participation in the screening programme is voluntary. It is generally believed that women who decide to participate in screening have a different baseline risk of breast cancer mortality to those who decide not to participate. This difference in baseline risk, expressed as a ratio, can be used to adjust the screening estimate from a case-control study (odds ratio (OR)).[9]

Results from the literature on the direction of self-selection are, however, inconsistent. Friedman and Dubin found that women who refused screening were at lower baseline risk for breast cancer death compared to a control group. Adjustment for this difference in baseline risk causes a larger screening effect (OR further from 1.0). In contrast, Moss et al. found the opposite, which would result in a smaller screening effect (OR closer to 1.0).[10-12]

It is to be expected that the factors underlying self-selection may be different in each country or even region that has implemented service screening. However, several studies have applied a correction factor based on estimates calculated from data from the Swedish and Canadian randomized controlled trials (RCT) by Duffy et al. instead of a country-specific or regionally determined selection factor.[3,13] Based on the study by Duffy et al., we anticipated a higher breast cancer mortality rate in the non-screened women. Therefore, the correction factor for self-selection has been estimated as the ratio of the IBM rate in the non-screened women and the IBM rate of the not-invited women.9 This ratio can then be applied to a formula to adjust the effect of breast cancer service screening on breast cancer mortality in a case-control study.[9,14]

When nationwide screening is offered to all women in the target group, a well-defined control group is no longer available. In this situation, the only period from which a control group can be created is directly before the start of the implementation of a screening programme or during the implementation of the screening programme, when part of the target group is still not-invited. The purpose of this study is to estimate a correction factor for self-selection bias from the implementation period of the service screening programme in five regions of the Netherlands, using the incidence-based mortality method (IBM).[15]

Methods

Service screening in the Netherlands started in 1989, initially inviting women in the age group 50-69 biennially, and was fully implemented in 1997. In this period nine screening organisations were responsible for the organisation of the screening programme. In this

study we included five regions, namely Stichting Kankerpreventie en –screening Limburg (SKsL), Stichting Kankerpreventie IKA (SKP IKA), Stichting Bevolkingsonderzoek Noord-Nederland (BBNN), Stichting Vroege Opsporing Kanker Oost-Nederland (SVOKON) and Stichting Bevolkingsonderzoek Borstkanker Zuidwest Nederland (SBBZWN). The regions were chosen based on their differences in urban and rural areas, and early and late implementation of the screening programme. These regions included 57% of the breast cancer patients in the age group 50-69 registered in the Netherlands Cancer Registry in the years 1990-1995.

An incidence-based mortality (IBM) rate can be calculated by dividing the number of breast cancer deaths resulting from incident breast cancer cases diagnosed in a specific period with the accompanying number of person-years. The calendar period for calculation of the IBM rate included the years 1990-1995. During the implementation phase of the Dutch screening programme, the female population in the targeted age group shifted from an uninvited population to an invited population, providing us with contemporaneous groups of not invited and invited but not screened women.

In order to define the numerator of the breast cancer mortality rates, data of breast cancer patients aged 50-69 and diagnosed in the years 1990-1995 were collected from the Netherlands Cancer Registry. The patient data were linked to the screening registries of the five screening organisations to collect information on screening history and vital status. The data were also linked with the Cause of Death Registry held by Statistics Netherlands to obtain cause of death. The breast cancer patients were divided in three groups according to their screening status: not invited for screening before diagnosis (not-invited), invited and screened before diagnosis (screened), invited and not screened before diagnosis (non-screened). Breast cancer patients were defined as not screened after not participating in the most recent invitation to screening before diagnosis. We followed the breast cancer patients for breast cancer death for a maximum of 10 years after date of diagnosis. Screened patients were not followed since this group does not contribute to estimation of the correction factor.

In order to define the denominator of the breast cancer mortality rates, we calculated the person-years for the period 1990-1995 using aggregated data on the total number of invited women, the total number of screened women derived from the screening organisations, and the age-specific total population derived from Statistics Netherlands. In order to divide the person-years in a group of not-invited and a group of non-screened person-years, we calculated the number of person-years during the implementation period of the screening in each municipality separately. The municipality is the smallest possible unit of which the starting date of screening was known. The population data and starting date of screening were determined and used in a previous study by Otto et al.[16] Further details on the calculation of person-years along with an example can be found in the appendix.

TABLE 5.1 Age at diagnosis and stage distribution for breast cancer patients divided to non-screened and not-invited patients

Breast cancer patients	**Non-screened N (%)**	**Not-invited N (%)**
Total	968 (100)	8979 (100)
Age at diagnosis		
50-54	236 (24.4)	2475 (27.6)
55-59	226 (23.4)	1948 (21.7)
60-64	225 (23.2)	2082 (23.2)
65-69	281 (29.0)	2474 (27.5)
Stage*		
0-1	296 (32.2)	2847 (33.6)
2+	623 (67.8)	5637 (66.4)

** for both groups 5% missing*

Results

In total, 15 541 breast cancers were diagnosed in women aged 50-69 in the period of 1990-1995. The complete number of person-years for this period was 5 199 451. Of the 8979 not-invited breast cancer patients, 2631 died of breast cancer, whereas of the 968 not screened patients, 345 died of breast cancer. *Table 5.1* shows patient characteristics of not-invited and non-screened women. The distributions of age at diagnosis (χ^2=5.03, df=3, p=0.17) and stage at diagnosis (χ^2=0.68, df=1, p=0.41) were comparable between both groups.

Data were available from five screening regions in the Netherlands. Poisson regression was used to test heterogeneity between the regions. The model which included the interaction terms of the regions fitted significantly better than the model without the interaction terms of the regions (χ^2=0.03), which points towards a difference in the degree of self-selection in the five regions.

Table 5.2 shows an example of the calculation of the IBM ratio in one region, namely the SVOKON region. The IBM rate in the non-screened women, 9.6 per 10 000 person-years, is somewhat higher than the IBM rate for the not-invited women, 8.8 per 10 000 person-years. Dividing those two IBM rates results in an IBM-ratio of non-screened versus not-invited of 1.08 (95% CI 0.85-1.37), indicating no self-selection in the SVOKON region.

In *Table 5.3*, the correction factors and their 95% confidence intervals of all regions are given. As for the SVOKON region, the SBBZWN and SKsL region showed no difference in breast cancer mortality risk between the non-screened and not-invited women. The IBM rate ratio in the BBNN and SKP IKA region is lower than one, indicating a lower breast cancer mortality risk in the non-screened women.

TABLE 5.2 Example of calculation of the incidence-based mortality (IBM) rates for non-screened and not-invited women in the region of SVOKON

SVOKON Period 1990-1995		
Non-screened		
	Incident cases	271
	Breast cancer deaths	99
	Person-years	103 358
	IBM / 10 000 PY	9.6
Not-invited		
	Incident cases	800
	Breast cancer deaths	216
	Person-years	244 204
	IBM /10 000 PY	8.8
Rate ratio* (95% CI)	(9.6/8.8)	1.08 (0.85-1.37)

** correction factor for self-selection, estimated by IBM rate non-screened / IBM rate not-invited*

TABLE 5.3 Correction factors for self-selection bias for five screening regions in the Netherlands

Region	**Breast cancer deaths / person-years**		**Rate ratio (95% CI)**
	Non-screened	*Not-invited*	
BBNN	36/73 412	702/917 668	0.64 (0.46 - 0.90)
SKP IKA	117/179 463	798/937 692	0.77 (0.63 - 0.93)
SKsL	39/63 341	189/282 716	0.92 (0.65 - 1.30)
SBBZWN	54/68 867	726/1 003 423	1.08 (0.82 - 1.43)
SVOKON	99/103 358	216/244 204	1.08 (0.85 - 1.37)

Discussion

The heterogeneity between the regions showed that even in a centrally organised screening programme regional differences can be found. Three of the five regions, namely the SBBZWN, SKsL and SVOKON regions, showed no difference in baseline risk in breast cancer mortality in women not participating to the Dutch screening programme compared to a not-invited population. In the BBNN and SKP IKA regions IBM ratios below 1.0 were found, representing a lower baseline breast cancer mortality risk in non-screened

to not-invited women. These ratios can be used as regional correction factors for self-selection bias for the odds ratio estimated in a case-control study to evaluate the impact of breast cancer screening on breast cancer mortality. Without correction in these two regions, the estimated breast cancer mortality reduction is slightly underestimated.

Looking at the magnitude of the correction factors and their confidence interval, heterogeneity is most likely a result of the 0.64 (95% CI 0.46-0.90) in the BBNN region. Reasons why this region is different from the other regions are not known. An explanation may be the higher attendance rate (83.9% compared to 78.9% nationally[17]) and a difference in underlying background risks for breast cancer mortality; it is the most rural area in this study. Furthermore, the use of aggregated person years could have influenced the heterogeneity. Between 1990 and 1995 many municipal borders were redrawn and municipalities renamed.[16] The precise division of the municipalities in the regions in this period is quite difficult to trace and some (differential) misclassification can have occurred.

The reason for a somewhat lower rate ratio in the BBNN and SKP IKA regions is not known. Studies that explored reasons for non-attendance in the Netherlands mentioned mammograms taken outside the service screening programme, practical reasons, pain, no breast cancer in the family and breast self-examination as reasons for not accepting an invitation to screening.[18,19] The possible association between these factors and a lower breast cancer mortality in non-screened women needs further exploration. A population survey performed in Australia also suggested that screening participants would have a slightly higher background risk of breast cancer than non-screened women. The participants were more likely to report a family history of breast cancer, a history of breast surgery, and previous use of hormone replacement therapy.[7] Using a proxy for self-selection bias like differences in risk factors or in incidence of breast cancer, is a way of coping with self-selection bias. However, caution is needed when interpreting the results. For example, it has been shown that equal breast cancer incidence in non-screened women and a control group does not necessarily lead to equal breast cancer mortality.[12]

In the region of SKsL we calculated a correction factor of 0.92 (95% CI 0.65-1.30) in this study. In a previous case-control study in the same region, we calculated a correction factor of 0.84 (95% CI 0.58-1.21).[20] There are two factors that might be responsible for this small change. First, we used a slightly different method to calculate the IBM-ratio. Instead of using date of diagnosis of each patient as start of follow-up, we had a start of follow-up time independent from date of diagnosis in the previous study. Second, a small difference in number of breast cancer deaths retrieved through linkage with the Cause of Death Registry of Statistics Netherlands could also be of influence. However, correction with these factors does not lead to a difference in impact of the breast cancer mortality reduction by breast cancer screening.

Our correction factors for self-selection calculated for the regions in the Netherlands differ from those used in other case-control studies. Duffy et al. calculated a correction factor for self-selection based on the data from RCTs of mammographic screening.[9]

This correction factor was 1.36, which represents a higher breast cancer mortality in the non-screened compared to the uninvited control group, and indicates a higher baseline mortality rate in the non-screened women compared to the screened women. The use of this correction factor is only justified when the relative mortality of the non-screened population and the population of uninvited women is the same in the programme at issue as observed in the previously published RCTs.[9] In recent case-control studies, the correction factor of 1.36 has been used to correct the odds ratio for self-selection bias.[3,13] Puliti et al. and Gabe et al. estimated regional or country specific correction factors of 1.11 and 1.17, respectively to correct the odds ratio.[4,6] In line with their results, our study demonstrates that 1.36 cannot be interpreted as a constant correction factor. Rather a country-specific or regionally determined correction factor should be used.

The application of date of diagnosis of each patient as start of follow-up was possible because we included non-screened and not-invited women only. When using a before-and-after the start of screening comparison for the effectiveness of screening, a date independent of diagnosis should be chosen to correct for possible lead time bias. Correction for lead time bias is only necessary if screened women are included in the comparison.[14,21,22]

Based on our study, the IBM method is an effective tool for calculating the correction factor for self-selection bias in the Netherlands. This is supported by a Swedish study, where they also calculated regional specific correction factors for self-selection bias using the incidence-based mortality method.[23] Our correction factor was based on breast cancer patients diagnosed in the period 1990 to 1995. Correction for self-selection bias of an estimated odds ratio for recent years would assume that the differential between the non-screened and not-invited women does not change over time. This assumption is inevitable, but is supported by the high and stable attendance rate in the Netherlands, which suggests that the non-screened women have not changed over time.

In conclusion, the heterogeneity between the regions shows the necessity for calculating regional or country specific correction factors, even in a centrally organised screening programme. Looking at the range of IBM ratios in the five screening regions, the odds ratio estimated in a nationally conducted case-control study will show no change or a small increase in breast cancer mortality reduction after correction for self-selection. This indicates that self-selection is only a minor problem in the Netherlands.

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Appendix

Calculation of person-years

The calculated number of person-years were based on the number of invited women, the number of screened women and the age-targeted female population for each municipality in the five regions separately. The not-invited number of person-years were calculated by subtracting the number of invited person-years from the total person-years of the targeted population.

The person-years of invited women were estimated based on the number of invited women:

- year of the start of screening: half of the number of invited women
- year+1: all invited women in the year of start of screening and half of the invited women in year+1
- year+2: 95% of the total population of that year, assuming that 5% of the eligible population is not-invited

Adding up the number of invited person-years for every municipality for the total period of 1990-1995 resulted in the total number of invited person-years.

In addition, the non-screened person-years were calculated by subtracting the screened person-years from the total number of invited person-years.

The number of person-years of the screened women were based on the number of screened women:

- year of the start of screening: half of the number of screened women
- year+1: all screened women in the year of start of screening and half of the screened women in year+1
- year+2: half of the screened women in the year of start of screening, all screened women in year+1 and half of the screened women in year+2

Adding up the number of screened person-years for every municipality for the period 1990-1995 resulted in the total number of screened person-years.

An example is given for one municipality (*Table 5.4 and Table 5.5*).

TABLE 5.4 Number of invited women, number of screened women and the number of the age-targeted female population for each year separately for municipality X

Year 1990	Female population 50-69	N = 430
Year 1991	Female population 50-69	N = 438
Year 1992	Female population 50-69	N = 457
	Invited women	N = 437
	Screened women	N = 375
Year 1993	Female population 50-69	N = 464
Year 1994	Female population 50-69	N = 487
	Invited women	N = 473
	Screened women	N = 405
Year 1995	Female population 50-69	N = 510

TABLE 5.5 Calculation of number of person-years for municipality X.
Start date screening = 1-9-1992

Municipality X	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**Total**
Total PY	430	438	457	464	487	510	2786
PY uninvited	430	438	238.5	27	24.3	25.5	1183.3
PY invited	-	-	218.5 (437*0.5)	437	462.7	484.5	1602.7
PY invited & screened	-	-	187.5 (375*0.5)	375	390	405	1357.5
PY invited & not screened	-	-	31	62	72.7	79.5	245.2

PY=person-years

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Breast cancer screening case-control study design: impact on breast cancer mortality.
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Chapter 6

Case-referent study design and the impact on breast cancer mortality

Abstract

Background – *Recent case-control studies on the effectiveness of population-based breast cancer screening show differences in the magnitude of breast cancer mortality reduction. We investigated the role played by aspects of the case-control study design on these differences, e.g. the definition of cases and exposure to screening.*

Material and Methods – *We investigated six case-control studies conducted in East Anglia (UK), Wales, Iceland, central and northern Italy, South Australia and the Netherlands.*

Results – *The breast cancer mortality reduction in the different case-control studies ranged from 38% to 70% in the screened versus the non-screened women. We identified differences in design, e.g. the inclusion or exclusion of the first years of screening, and the correction factor for self-selection bias.*

Conclusions – *Overall, the design of the case-control studies was similar. The differences in the magnitude of breast cancer mortality reductions are therefore unlikely to be caused by variations in the design of the case-control studies. These differences must be due to other factors, like the organisation of the service screening programme and the attendance rate. The reduction in breast cancer mortality estimated in these case-control studies indicates that the impact of current mammographic screening is at least consistent with the effect reported by the former randomised screening trials.*

Introduction

Recently, several case-control studies have been conducted to estimate the effect of population-based service screening programmes.[1-4] Their results show a decrease in breast cancer mortality which is at least consistent with the results of the randomised controlled trials (RCTs) conducted in the 1970s and 1980s. However, the magnitude of the effect, expressed in the odds ratio (OR), varies substantially between the different studies. We investigated the role of variations in the design of case-control studies on the differences in estimated effects of population-based breast cancer screening on breast cancer mortality.

Population-based screening aims to identify each eligible woman in the target population in the area served by a screening programme and to personally invite them to each organisational round of screening.[5] Continuous monitoring of the programme is required to better understand the positive results of screening and the negative outcomes, e.g. the number of false-positive screening outcomes. In addition, changes over time in baseline risk for breast cancer, screening methods and therapy also necessitate a periodic reassessment of efficacy.

A case-control study is an efficient method for estimating the benefit of cancer screening.[6] In 1986, Sasco et al.[7] suggested that a routine case-control assessment of the functioning of a mass screening programme could be, or even should be, an integral part of ongoing evaluation. The use of a case-control study includes a number of methodological challenges, like the definition and selection of cases and controls, the definition of exposure to screening and self-selection bias.[8]

Conducting a case-control study begins with defining the source population. A source population should include women who have died of breast cancer (cases), women who have not died of breast cancer (controls) and population-based screening must be available to all members of the source population.[9] The use of death certificates is a valid way of classifying breast cancer as the underlying cause of death for the cases.[10-12] Controls should be selected from the source population that generated the cases. Furthermore, they should be free of breast cancer at the time of diagnosis of the case and should be alive at time of death of the case.[9,13] Care must be taken to ensure that the cases and controls have an equal opportunity for screening.[8] After identifying the cases and controls, the screening history of the cases is compared with the screening history of the controls. If screening is effective, the cases have had less exposure to screening than the controls.

Self-selection bias has received a great amount of attention when using case-control studies for measuring the effectiveness of screening. It refers to the possible difference in baseline risk for breast cancer death a priori for women who accept the invitation to screening compared with those who do not accept the invitation to screening.[8] In the literature, contradictory results have been noted with regard to the direction and

magnitude of self-selection. Where Friedman and Dubin found that women who accepted screening were at higher baseline risk for breast cancer mortality compared with a control group, Moss et al. found the opposite.[8,14,15]

Material and methods

Literature search

A PubMed search was carried out for the period 2000 to 2010 to identify recent publications written in English on case-control studies that assessed the effect of a breast cancer service screening programmes in steady state on breast cancer mortality. A study was included if it fulfilled the following conditions: the case-control studies had to be based on population-based screening programmes and had to include breast cancer deaths occurring in the steady state of screening, which we defined as breast cancer deaths after the year 2000.

The following search strategy was used: 'mass screening' [mesh] and ('case-control studies' [mesh] or 'case–referent') and 'breast neoplasms/epidemiology' [mesh]. We manually searched the bibliographies of recent reviews of the evaluation of service screening on breast cancer mortality for additional references.[16-18] In total, 121 studies were retrieved. Titles and, if necessary, abstracts found through the search strategy were evaluated for potential relevance.

Six articles of recent case-control studies in population-based service screening countries were identified: East Anglian region (UK) (Allgood et al.[1]), Wales (Fielder et al.[19]), Iceland (Gabe et al.[2]), the Netherlands (Paap et al.[20]), central and northern Italy (Puliti et al.[3]), and South Australia (Roder et al.[4]). From this point on, we refer to these studies using the name of the first author.

Design aspects of case-control studies

We focused on five design aspects of the selected case-control studies, which could influence the magnitude of the estimated ORs: the source population, the selection of cases, the selection of controls, the definition of exposure to screening and correction for potential selection bias.[8,13,21] If information was not available in the paper, we contacted the first author. The design of the six case-control studies is presented in *Figure 6.1*. In *Figure 6.1*, a timeline represents the change from a not-invited population to an invited population (source population) after the start of the implementation of a screening programme. From this invited population, a case and control were selected who both have a screening history from which the effectiveness of breast cancer screening can be estimated.

Source population. According to the source population, we looked at differences in the age of invitation, e.g. women aged 40–49 years are not included in every country. This

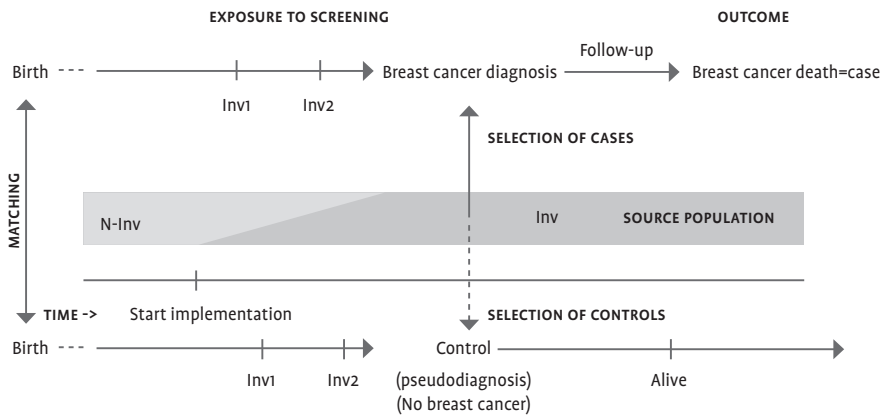

FIGURE 6.1 Design of the case–control studies for screening. Inv1, invitation 1 of case and control; Inv2, invitation 2 of case and control; N-Inv, not-invited women; Inv, invited women.

can lead to a different estimate of the impact of the screening programme. It is likely that breast cancer screening has less impact on breast cancer mortality in women aged 40–49 years compared with those aged 50–69 years. Including women aged 40–49 years in the analysis will therefore result in an OR closer to 1.

Selection of cases. A distinction is made between primary breast cancer deaths (breast cancer as underlying cause of death) and secondary breast cancer deaths (breast cancer present at death). Inclusion of primary breast cancer deaths alone can give different results than when secondary breast cancer deaths are included; in this last case, the effect of screening is probably diluted.

An optimal screening effect is not achieved in the first years of screening because prevalent screen-detected cases benefit less.[22] Prevalent screen-detected cases are women diagnosed in the first round of screening or in a woman's first test at a subsequent round.[23] Therefore, they dominate the first years of the implementation of screening programmes. Excluding breast cancer diagnosis and breast cancer deaths during the first years of implementation from the case-control study results in an estimate of the steady state of the screening programme.

Selection of controls. For the controls, we focused on the methods used to ensure that they had the same opportunity for screening as the cases.

Definition of exposure to screening. The time window for including screening history should be limited to the detectable preclinical period (DPCP).[8,24] Including screening examinations outside the DPCP can distort the effect of screening. Therefore, differences

in the time window of screening exposure can lead to differences in outcome. Etzioni and Weiss[21] found that underestimation of the duration of the DPCP leads to greater bias than overestimation. Both are expected to bring the OR closer to 1.[21,25]

Correction for selection bias. In the six case-control studies, we checked which method and correction factor was used to correct for self-selection bias, e.g. the method and correction factor of Duffy et al.[26] Duffy et al. calculated a correction factor of 1.36 based on the relative rate of breast cancer deaths in non-attenders in the Two-County, Malmö, Gothenburg, Stockholm and Canadian national breast screening RCTs compared with women in the control arm of these RCTs.

Adjustment for socioeconomic status (SES) can contribute partly to the amount of self-selection bias.[19] As there is a correlation between SES and breast cancer risk, differences in SES in screened and nonscreened women are likely to have an influence on the effect estimate.[27,28]

Results

The start of the service screening in the countries of the six identified case-control studies was between 1987 and 1990. *Table 6.1* provides details of the relevant background information of the service screening in each country. *Table 6.2* shows an overview of the results of the analysis of women who attended screening compared with those who did not attend screening. The mortality reduction ranged from a minimum of 38% in Wales (OR 0.62, 95% confidence interval (CI) 0.47–0.82) to a maximum of 70% in the Netherlands (OR 0.30, 95% CI 0.14–0.63). These results do not include any corrections for self-selection.

Source population. All programmes invite women aged 50–69 years, with the exception of Wales, which invites women aged 50–64 years (*Table 6.1*). The UK and Australia allow women over 70 years to come to the screening, whereas the Netherlands actively invites women aged up to 74 years. Women aged 40–49 years are actively invited in Iceland and are allowed to take part in the service screening in Australia.

Selection of cases. Four case-control studies included primary breast cancer deaths only. Allgood and Fielder also included secondary breast cancer deaths (*Table 6.3*). The ORs calculated by Allgood and Fielder, 0.35 and 0.62, respectively, were no different to the other four studies. Allgood, Paap and Roder restricted the years of breast cancer diagnosis and the time period of breast cancer deaths, thereby excluding the prevalent cases in the years of the implementation of the screening programme. Allgood and Paap showed the lowest ORs of all case-control studies.

TABLE 6.1 Background of the service screening programmes in the case-control studies

Country	UK	Wales	Iceland	Netherlands	Italy	Australia
Case-control study	Allgood et al.[1]	Fielder et al.[19]	Gabe et al.[2]	Paap et al.[20]	Puliti et al.[3]	Roder et al.[4]
National screening	Yes	Yes	Yes	Yes	No	Yes
Cancer registry	Yes	Yes	Yes	Yes	Yes	Yes
Background Incidence[a], ASR (W)/100 000	76.4 (1988-1992)	68.8 (1988-1990)	79.0 (1988-1992)	79.6 (1989-1992)	67.0 (1988-1991)	68.5 (1988-1992)
Area of case-control study	East Anglian region	Wales	Iceland	Southeast Netherlands	Northern and central Italy	South Australia
Year of start screening	1989	1989	1987	1990	1990	1989
Implementation complete in studied region	1989	1991	1989	1994	1994–1998	1994
Age invited	50–70 active, 70+ allowed	50-64	40-69	50-74	50-69	50-69 active, 40-49 and 70+ allowed
Screening interval (years)	3	3	2	2	2	2
Attendance rate	75%[b]	77%	61%-62%	82%	65%	57%[c]

[a] *Parkin DM, Whelan SL, Ferlay J, Storm H. Cancer Incidence in Five Continents, Vol. I to VIII. IARC CancerBase No. 7, Lyon, 2005.*
[b] *www.cancerscreening.nhs.uk*
[c] *www.cancerscreening.gov.au*

TABLE 6.2 Effect estimate for ever/never screened, screened at the index invitation, number of screens and time since last screen

Study	Country	Ever–never, OR (95% CI)	Index invitation	Number of screens		Time since last screen (years)	
Allgood et al.[1]	UK (East Anglian region)	0.35 (0.24–0.51)		None	2.51 (1.56–4.03)	Never	1.71 (1.03–2.80)
				1	1	<1	1
				2	0.70 (0.43–1.11)	1–2	0.43 (0.24–0.77)
				3+	1.03 (0.59–1.77)	2–4	0.48 (0.28–0.81)
						4+	0.55 (0.29–1.04)
Fielder et al.[19]	Wales	0.62 (0.47–0.82)		None	1	Never	1
				1	0.65 (0.48–0.88)	<0.5	1.57 (0.92–2.70)
				2	0.64 (0.43–0.96)	0.5–1	0.43 (0.22–0.85)
				3+	0.38 (0.19–0.72)	1–2	0.42 (0.25–0.68)
						2–4	0.59 (0.39–0.89)
						4+	0.58 (0.36–0.93)
Gabe et al.[2]	Iceland	0.59 (0.41–0.84)		None	1	Never	1
				1	0.60 (0.40–0.90)	<2	0.63 (0.43–0.91)
				2	0.63 (0.38–1.03)	2–3	0.68 (0.36–1.30)
				3	0.42 (0.22–0.80)	3–5	0.42 (0.18–0.96)
				4	0.67 (0.31–1.42)	5+	0.38 (0.18–0.88)
				5+	0.61 (0.21–1.74)		
Paap et al.[20]	Netherlands (IKL region)		0.30 (0.14-0.63)				
Puliti et al.[3]	Italy	0.46 (0.38-0.56)					
Roder et al.[4,a]	Australia	All ages: 0.59 (0.47-0.74)		Frequent[b]	0.47 (0.34-0.65)	≤ 3	0.57 (0.44-0.72)
		Age 50-69: 0.54 (0.41-0.72)		Other	0.64 (0.50-0.82)	> 3	0.70 (0.47-1.05)

[a] *Number of screens and time since last screen corrected for SES and health service access.*
[b] *Frequency of recent screening: ≥3 screening rounds at ≤30-month intervals immediately preceding diagnosis.*
CI, confidence interval; IKL, Comprehensive Cancer Centre Limburg; OR, odds ratio; SES, socioeconomic status

TABLE 6.3 Design aspects of recent case-control studies

Country	**UK**	**Wales**	**Iceland**	**Netherlands**	**Italy**	**Australia**
Case–control study	Allgood et al.[1]	Fielder et al.[19]	Gabe et al.[2]	Paap et al.[20]	Puliti et al.[3]	Roder et al.[4]
Cases						
Number	284	419	226	118	1750	491
Breast cancer deaths	Primary or secondary[a]	Primary or secondary	Primary[b]	Primary	Primary	Primary[b]
Death certificate	Yes	Yes	Yes[b]	Yes	Yes	Other[b,c]
Time period breast cancer deaths	1995–2004	1998–2001	1990–2002	2004 or 2005	1988–2002	2002–2005
Restriction for years of diagnoses	From 1995	From 1991	From start service screening	From start service screening	From the year before start of service screening	From 1994
Controls						
Number	568	717	902	118	7000	1473
Matchingvariables	Date of birth	Year of birth, one from same GP, one from other GP	Date of birth, area of residence[d]	Year of birth, area of residence at index invitation of case	Date of birth, area of residence	Date of birth
Matching factor	1 : 2	1 : 2 or 1 : 1	1 : 3 or 1 : 4	1 : 1	1 : 4	1 : 3
Screening exposure	Ever/never attendance before (pseudo) diagnosis	Ever/never attendance before (pseudo) diagnosis	Ever/never attendance before (pseudo) diagnosis	Screened at index invitation	Ever/never attendance before (pseudo) diagnosis	Ever/never attendance before (pseudo) diagnosis

[a] *In the paper of Allgood contributory is used instead of secondary.*
[b] *Personal communication with first author.*
[c] *The decision on cause of death was made by cancer registry staff using death records, clinical extracts from hospital records, pathology records and occasionally consultation with treating clinicians.*
[d] *In the paper of Gabe screening area is used instead of area of residence.*
GP= general practitioner

Selection of controls. Five case-control studies used a pseudo diagnosis for each control, which was equal to the date of diagnosis of that control's matched case (Allgood, Fielder, Gabe, Puliti and Roder). To ensure an equal opportunity for screening, in the design phase, Puliti postponed the pseudo diagnosis for the controls matched to screen-detected cases by 1 year to compensate for lead time in the screen-detected cases.[29] Fielder did the same, but then as a secondary analysis and with a postponement of 18 months. This had no effect on the OR. Paap corrected for opportunity for screening by making sure that the control was invited for the same screening round from which the index invitation of the case emerged. In Gabe's study, the correction for opportunity was based on a calculation described by Duffy et al.[30]

Exposure to screening. Primary analysis of the case-control studies was based on the complete screening history before diagnosis (case)/pseudo diagnosis (control); the ever/never comparison (*Figure 6.1*). Paap used an index invitation for exposure, which was defined as the invitation date closest to the date of diagnosis of the case.

Correction for selection bias. In all articles, corrections for self-selection bias were made using the method described by Duffy et al.[26] (*Table 6.4*). Allgood and Fielder used the same correction factor as Duffy et al. (1.36). Roder mentioned in the discussion that the adjusted OR for self-selection using Duffy's formula et al. would be around 0.70, thus indicating a 30% mortality reduction instead of 41% reduction with no correction for self-selection.

Instead of using the correction factor of 1.36, Gabe, Puliti and Paap used an area-specific correction factor, which were 1.17, 1.11 and 0.84, respectively. Gabe (personal communication with first author) calculated their correction factor as being the relative risk of breast cancer death for non-attenders compared with the uninvited population from the RCTs as estimated in the paper by Duffy et al.[26] Puliti used a group of not-yet-invited women, which was available because of the long implementation period of the service screening in Italy. They compared the OR in the never respondents with that in the not-yet-invited. Paap used the incidence-based mortality method as a tool to calculate a correction factor for self-selection.[23] They calculated the incidence-based mortality for a group of women not-yet-invited during the implementation period of screening and compared this with the incidence-based mortality for the not-screened women in the same period. Corrections for SES were carried out by Allgood, Fielder and Roder and showed no alterations to the ORs.

TABLE 6.4 ORs corrected for self-selection bias

Study	Country	Crude, OR (95% CI)	Factor Duffy 1.36	Using own factor correction factor	SES
Allgood et al.[1]	UK (East Anglian region)	0.35 (0.24-0.51)	0.52 (0.32-0.84)		0.35 (0.23-0.51)
Fielder et al.[19]	Wales	0.62 (0.47-0.82)	0.75[a] (0.49-1.14)		No difference
Gabe et al.[2]	Iceland	0.59 (0.41-0.84)		0.65 (0.39-1.09), is adjusted for opportunity bias as well (Factor = 1.17, 95% CI 1.08-1.26)	
Paap et al.[20]	Netherlands (IKL region)	0.30 (0.14-0.63)		0.24 (0.10-0.58) (Factor = 0.84, 95% CI 0.58-1.21)	
Puliti et al.[3]	Italy	0.46 (0.38-0.56)		0.55 (0.36-0.85) (Factor = 1.11, 95% CI 0.87-1.40)	
Roder et al.[4]	Australia	0.59 (0.47-0.74)	0.70		0.59 (0.47-0.74), is adjusted for health service access as well

[a] *Did only correct for self-selection on tumours diagnosed in 1995-2001, where the crude OR was 0.49 (0.36-0.66).*
CI, confidence interval; OR, odds ratio; SES, socioeconomic status

Discussion

Our study focused on the impact of differences in the design of recent case-control studies on the effect of breast cancer mortality in population-based breast cancer screening programmes. Although we found many minor differences in the set up of the six case-control studies, the overall design was quite similar. However, the range of the mortality reductions in the different case-control studies was large: from 38% reduction in Wales to 70% reduction in the Netherlands.

Looking at the differences in invited age groups, women aged 40–49 years were only included in the studies by Gabe and Roder. Roder included a stratified analysis of the effect of different age groups, which showed an OR of 1.18 in the age group <50 years and an OR of 0.54 (*Table 6.2*) in the age group 50-69 years. The change from an OR of 0.59 for all ages to an OR of 0.54 for the age group 50-69 years indicates that age of invitation plays no key role in the difference of the estimated OR in Australia compared with the other countries. A reason for this could be that there are fewer cases in the 40-49 age group than in those aged 50-69 years. Therefore, the OR of 0.59 will mainly consist of results for the latter group. Gabe did not show any age-specific results, but a large change in OR is not expected for the proportionally small numbers found in the younger age group.

A difference between the screening case-control studies is the inclusion or exclusion of the first years of screening. Analysis of the steady state gives lower ORs than the studies which included the first rounds of screening. This is also demonstrated in Fielder's study, where the OR including diagnosis in the early years of screening was 0.62 (95% CI 0.47-0.82) and the OR excluding diagnosis in the early years of screening was 0.49 (95% CI 0.36-0.66). Excluding the early years of screening in the studies by Gabe and Puliti will probably bring the effect on breast cancer mortality closer to the effect found by Allgood and Paap. Roder, however, did not find a large impact of the service screening programme compared with Allgood and Paap. This could perhaps be due to the lower attendance rate in Australia (57%) compared with the UK (75%) and the Netherlands (82%).

All case-control studies aimed to ensure an equal opportunity for screening for both the controls and the cases. Fielder showed no alteration in the OR. A sensitivity analysis carried out by Puliti for time lags of 6 months and 1.5 years instead of 1 year showed only small alterations in the OR. Gabe showed a change in the OR from 0.59 (95% CI 0.41-0.84) to 0.51 (95% CI 0.31-0.86) after correction for opportunity for screening, thus only a small change in the OR. Gabe based his correction on a method developed by Duffy et al.[30] Using the correction method of Duffy et al. will already partly adjust for the prevalent screens in the first years of screening. The study by Duffy et al. also corrected the OR of Fielder for opportunity for screening using the same method, which did not lead to a change in the OR. These results show that the impact of opportunity for screening on the magnitude of the OR is limited.

The analyses for exposure to screening are similar in all case-control studies except Paap, who used exposure to the index invitation as their primary analysis instead of using the ever/never comparison. The screening history should be limited to the period when the cancer is potentially detectable on the mammogram – in the DPCP. The exact duration of the DPCP is not known, but in the future, when service screening has been running for a longer period, the ever/never comparison will overestimate the length of the DPCP, which would cause a false reduction of the size of the benefit of screening.[21,25] By only using the index invitation, Paap has probably underestimated the length of the DPCP. Extending the exposure to screening, to the invitation preceding the index invitation, resulted in a small change in mortality reduction from 70% to 73% (OR 0.27, 95% CI 0.12-0.62).

By correcting the OR for self-selection bias using the correction factor of 1.36 calculated by Duffy et al., two assumptions are made: the relative mortality in the noncompliers compared with the not-yet-invited is the same in the service screening programmes as it is in the RCTs and self-selection in Sweden and Canada is the same as in the countries where the case-control studies are carried out. This may not hold for most populations. For example, a high attendance rate, like in the two-county trial, will make the group of women not attending the screening more special.[26] The area-specific calculated correction factors did not indicate a very high impact of self-selection on service screening compared with no impact of self-selection (OR 1). The correction factor for Italy calculated from not-yet-invited cases and never-screened cases was 1.11 (95% CI 0.87-1.40), the correction factor of Gabe was 1.17 (95% CI 1.08-1.26) and the correction factor of Paap calculated from the incidence-based mortality method was 0.84 (95% CI 0.58-1.21).

The adjustments for SES had no effect on the ORs of the case-control studies, indicating a minor influence of self-selection bias on the effect estimate of screening on breast cancer mortality as well. Furthermore, to assist the interpretation of the case-control study, Roder also included a population survey to identify potential differences in risk profiles by screening participation. This survey showed that predictors for screening participation were a higher number of first-degree female relatives with a history of breast cancer, exposure to hormone replacement therapy and a history of breast surgery for any reason. This suggests that screening participants may have a higher background risk for breast cancer than non-participants. On the other hand, Lawrence et al. showed that the 10-year relative survival rate in never attenders (51.9%) was lower than the survival rate in women diagnosed before invitation (67.6%). This was in contrast with the survival rate of occasional non-attenders, who had a relative survival rate of 66.9%.[31] This indicates that the correction factor for self-selection is influenced by the type of non-attender as well.

So it seems that the correction factor of 1.36 is not valid in other screening programmes to correct for self-selection and should not be used in future case-control studies. Instead, region- or country-specific correction factors for self-selection should be estimated. More emphasis should be placed on exploring methods like the incidence-based mortality

method to calculate differences in the underlying breast cancer mortality risk in the screened and not-screened populations to determine the impact of self-selection in the service screening.

Overall, the design of the six case-control studies was similar. However, inclusion of the first years of screening and the correction factor used to correct for self-selection bias can probably explain some of the differences in the magnitude of the effect in the recent population-based case-control studies. Other factors must influence the ORs of the case-control studies, e.g. differences in attendance rate, in the quality and organisation of the screening programme and in the quality of treatment. The range of obtained mortality reduction was 38%-70% in the six case-control studies (25%-76% after correction for self-selection). This indicates that the impact of current mammographic screening is at least consistent with effect (25%-30%) reported by the former randomised screening trials.

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Chapter 7

Effectiveness, the case-referent design and what's next

Breast cancer screening programmes have been implemented in many Western countries to reduce breast cancer mortality. However, the benefits achieved by these programmes are still an extensive topic of debate.[1,2] Very recently the discussion on the effectiveness of screening has been given impetus as a result of negative articles published in high impact journals.[3-5] The opponents of breast cancer screening state that the mortality reduction achieved by screening is only minor and they question the balance of benefits and harms. The results of this thesis show that screening brought about a significant 58% reduction of breast cancer mortality in screened versus unscreened women (58% reduction, 95% CI 47%-67%), indicating that the Dutch breast cancer screening programme is highly effective.

We have shown that the case-referent study is a valid and feasible tool to monitor the association between breast cancer screening and breast cancer mortality, if comparability between screened and unscreened women is guaranteed. It is essential to correct the odds ratio emerging from the case-referent study for self-selection bias, if present. To this end, we used the incidence-based mortality method to calculate the differential in breast cancer mortality between the group of unscreened and the group of not-invited women.

Validity of the case-referent design

We believe that the case-referent design is the most appropriate methodology to estimate the actual benefit of the current screening programme. However, not everyone is convinced of the validity of the results from the case-referent design. This is illustrated by a response from a Journal Editor based on a recent submission: '*... randomized designs will likely generate much more robust and unbiased estimates of effect than case-control or cohort studies*'. Or even worse, in a reply letter to a case-referent study conducted in Nijmegen, the method used was described as flawed.[6] Randomised controlled trials (RCTs) are considered the 'gold standard' research design. However, after nationwide implementation of a screening programme, only observational designs are available for estimating the effectiveness of screening programmes. It has been demonstrated that well-designed case-referent studies provide equally valid results regarding the magnitude of breast cancer mortality reduction.[7-11]

In RCTs the effect of screening is measured by comparing women invited versus women uninvited to the screening programme (intention to treat estimate). The magnitude of the effect estimate in the RCTs is influenced by the attendance rate of the invited women. In case-referent studies screened women are compared with unscreened women, thereby resulting in a larger effect estimate of screening. The odds ratio resulting from a case-referent study can be translated into an intention to treat estimate. In the Netherlands translation to an intention to treat estimate based on an attendance rate of 80% still results in a larger mortality reduction compared to the early trials (48% reduction, 95% CI 39%-56%; Chapter 4). This could be explained by improvements in the quality of service screening over time and a larger combined effect of early detection and improved treatment.[12]

In the scientific literature, many papers have been written on the methodology of case-referent studies for the evaluation of cancer screening.[13-16] International agreement has been reached about the correct methodology for conducting a case-referent study, as demonstrated by the comparability of the designs of recently conducted case-referent studies (Chapter 6).[17] Some differences in the design were identified, of which the most important were the in or exclusion of the first years of screening and the source population from which the correction factor was derived to address self-selection bias.

In Chapter 5 we showed that for the five large screening regions included in our studies the magnitude of self-selection varied.[18] This illustrates that the estimation of a national and even region specific estimate for self-selection is an important part of conducting a case-referent study. For the five regions, we demonstrated that self-selection bias only plays a minor role in the overall effectiveness estimate of breast cancer screening. We advise to estimate regional specific correction factors for future regional evaluations in the Dutch regions not included in this study.

Furthermore, confounding bias of the odds ratio can occur when prevalence of a risk factor for breast cancer death is imbalanced across the compared groups. Age is strongly related with both the occurrence of breast cancer death and screening participation. It is therefore necessary to adjust the effect estimate for age by matching beforehand or in the analysis afterwards. In this thesis we matched for age, thereby correcting for the influence of this confounder. Other than age there was no background information available on other possible risk factors for breast cancer in our dataset. Risk factors like mammographic density, socioeconomic status and obesity could theoretically distort the relation between breast cancer screening and breast cancer mortality. However, we demonstrated that residual confounding after adjustment for age is a minor issue in the evaluation of screening programmes.[19] Therefore, we assume that any other confounding factors will not greatly affect the estimated benefit of the screening programme.

Another point for discussion is that some researchers are not convinced that the use of primary breast cancer death as an endpoint is a reliable measure.[20,21] In our studies the outcome measure was primary breast cancer death based on death certificates documented in the Cause of Death Registry. Based on evidence from different countries, the Health Council of the Netherlands concluded in 2002 that the use of death certificates is valid for use as an end point for the evaluation of the screening programme, as the misclassification rate is modest and is not affected by mode of detection.[22-26]

What's next?

The case-referent design is an appropriate monitoring tool for future periodical evaluations of breast cancer screening effectiveness. Conducting a case-referent study will become easier with the current availability of the nationwide databases of the Netherlands Cancer Registry and the screening organisations. The introduction of a

nationwide unique identifier, the Civil Service Number (Burger Service Nummer, BSN) in the registries of screening organisations, cancer registry and Statistics Netherlands will also greatly improve the linkage of individual data from different registries to each other, both in terms of efficiency as well as quality due to less uncertainty about proper linkages. Unfortunately, at this moment The Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens, WBP) states that the BSN may not be used for research purposes.

In addition, the case-referent design should be used if changes and improvements over time in the field related to breast cancer screening are expected to have an influence on breast cancer mortality, like changes in incidence of breast cancer or improvements in treatment. The odds ratio, emerging from the case-referent study is a result of the combination of early detection followed by appropriate treatment. Assuming that the applied treatment depends on the stage of disease at diagnosis, treatment is somehow an intermediary in the relation between screening and breast cancer mortality. If future improvements in treatment come to a point where breast cancer can be treated more effectively at any stage, the difference in stage specific survival will decline, which will have an effect on the estimated odds ratio.[27]

A current example of improved technology is the implementation of digital mammography in the Dutch screening programme, which started in 2008 and was completed in 2010. It is expected that digital screening will lead to further reduction of breast cancer mortality, because of an improved detection rate. This improvement is most prominent in the initial screening examinations, i.e. for the youngest women of the screening population.[28-30] Improvements in the screening programme need a long follow-up time to measure further reductions in breast cancer mortality as a result of earlier cancer detection. Therefore, a period of ten years is required between the conducted case-referent studies. Further to the case-referent studies conducted in this thesis, this would mean that in a future case-referent study, cases are included who died up to and including 2015. Some of these cases will have been screened digitally and some analogously, because the majority of the cases will have been diagnosed in the ten years before they died.

Self-selection bias

All future case-referent studies should address the application of a correction factor for self-selection. For our calculations we used data from the implementation period of the screening programme in the Netherlands. Only before nationwide implementation is it possible to compare a group of not screened women with a group of not-invited women. Thus in the Netherlands, no more recent correction factors for self-selection can be estimated. By using the correction factor for the period 1990-1995, the assumption is made that the differential in baseline mortality risk has not changed over time. Given the stable attendance rate in the Netherlands we expect this assumption to be valid. However, future changes in attendance rate or risk factors which might influence the differential in breast cancer mortality risk between screened and unscreened women might change the plausibility of the correction factors based on the years 1990-1995.

There are two options for indicating whether these correction factors remain plausible over time. The differential of the annual incidence rates of breast cancer for screened and unscreened women should remain unchanged. This differential can be used as a monitoring tool to look for major changes. Another option for the evaluation of the baseline risks for breast cancer death of screened and unscreened women, could be the collection of information on risk factors for breast cancer mortality, like the registration of mammographic density following screening examinations.[31,32] Differences in incidence and risk factors do not necessarily lead to an equal translation to differences in breast cancer mortality between screened and unscreened women, and the results need to be interpreted with caution. For example, it has been shown that equal breast cancer incidence in unscreened women and a not invited control group based on data from the United Kingdom trial does not necessarily lead to equal breast cancer mortality, because of a tendency for breast cancers in unscreened women to have a poor prognosis relative to those in the comparison population.[11] A further understanding of these possible indicators for self-selection bias and coping with the problems they raise is essential for the future use of case-referent studies.

Communication

The information resulting from a case-referent study is relevant for communicating the level of risk reduction a woman may expect when participating in the screening programme.[9,33] The results of our study add valuable and not previously known information about this risk reduction in the Netherlands: women who attend the Dutch screening programme halve their risk of dying from breast cancer (OR = 0.42, 95% CI 0.33 to 0.53).

To understand the impact of the screening programme absolute numbers are generally more easy to understand than the relative effect measure coming from the case-referent design. Translation of the odds ratio estimated in this thesis to an absolute number needs careful consideration, because it will be based on a number of assumptions.[34,35] Moreover, graphical displays of information instead of numerical data may substantially improve comprehension of risk.[36,37] The research field of communication strategies in screening programmes is large and beyond the scope of this thesis.[38,39]

Most importantly, communicating the benefit of the Dutch screening programme expressed as the effect estimate of the case-referent design needs to be done in a clear, proper and balanced way to the women invited to the screening programme.

A well matched pair!

Based on our results, we conclude that the case-referent design is the preferred tool for monitoring breast cancer mortality reduction due to screening with the provision that a reliable correction for self-selection bias is available. For the evaluation of the Dutch breast cancer screening programme now and in the future, breast cancer screening effectiveness and the case-referent design are a well matched pair.

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Summary

The Dutch breast cancer service screening programme has now been running for 20 years. The current breast cancer mortality reduction can differ from results generated from the pilot programmes and randomised controlled trials on which the programme was implemented. To estimate the benefit of screening, i.e. the preventable fraction of breast cancer deaths, the case-referent design is an appropriate tool, if specific methodological complexities are allowed for. As such, the case-referent study was tested as a monitoring and evaluation tool for assessing the ongoing programme. To address this, we estimated the impact of screening mammography at both regional and national level, using individual data directly linking screening history with breast cancer death. In addition, we calculated regional correction factors for self-selection bias, estimated with data from the implementation phase of the screening programme, using the incidence-based mortality method. Furthermore, we investigated whether differences in the designs used explained the differing mortality reductions from recently conducted case-referent studies. Because the impact of screening on mortality is dependent on the incidence in the population, we estimated changes in lifetime risk over the past two decades.

Lifetime risk

The lifetime risk represents the average risk at birth that a Dutch woman will develop breast cancer or die from breast cancer during her lifetime. We found that the lifetime risk for developing breast cancer (both invasive and carcinoma in situ) has increased from 1 in 10 in 1989 to 1 in 7 in 2003. The risk of dying from breast cancer has decreased respectively from 1 in 22 to 1 in 26.

Effectiveness

Breast cancer screening trials conducted in the 1970s and 1980s resulted in a breast cancer mortality reduction of 25-30% in those offered mammographic screening. On the basis of these trial results, mammographic screening programmes were implemented in many Western countries in the 1990s to reduce the burden of breast cancer mortality. Nevertheless, the benefits are still subject to debate: whether the mortality reduction is large enough to justify the harms of screening. To assess the effect of screening on breast cancer mortality reliably, it is necessary to directly link a woman's cause of death and her screening history. We applied the case-referent design to evaluate the effect of the current Dutch population-based screening programme. The odds ratio (OR), emerging from the case-referent study, was adjusted for self-selection bias using regional correction factors for the difference in baseline risk for breast cancer death between screened and unscreened women.

In a case-referent study conducted in the province of Limburg, analysis of the data showed a breast cancer mortality reduction of 70% in the screened versus unscreened women (OR = 0.30, 95% CI 0.14 to 0.63]. After correction for self-selection bias, the effect of screening increased to 76% (OR = 0.24, 95% CI 0.10 to 0.58]. In the nationwide case-referent study, we found that attending the screening programme resulted in a 58% reduction in breast cancer mortality (OR = 0.42, 95% CI 0.33 to 0.53). In conclusion, the current Dutch breast cancer screening programme is achieving a substantial reduction in breast cancer mortality.

Self-selection bias

A problem associated with case-referent studies is the possible influence of self-selection bias on the magnitude of the effect of screening. Participation in the screening programme is voluntary. It is generally believed that women who decide to participate in screening have a different baseline risk of breast cancer mortality to those who decide not to participate. This difference in baseline risk, expressed as a ratio, can be used to adjust the screening estimate from a case-control study (OR). Using the incidence-based mortality method (IBM), a correction factor for the potential influence of self-selection can be derived from a group of unscreened women and a group of not-invited women.

Incidence-based breast cancer mortality rates according to screening status were calculated for five screening regions in the Netherlands. Heterogeneity between the regions was shown, which stresses the importance of a country- and/or region-specific estimate of self-selection. Adjusting for self-selection bias in the regional case-control studies would not change the breast cancer mortality reduction in three regions and would result in an even larger effect in two regions. Looking at the range of IBM ratios the overall influence of self-selection in the Netherlands is minor.

Differences in case-referent designs

Recent case-referent studies on the effectiveness of population-based breast cancer screening show differences in the magnitude of breast cancer mortality reduction. We investigated the role of variations in the design of the case-referent study on the differences in estimated effects. We included six case-referent studies conducted in East Anglia (UK), Wales, Iceland, central and northern Italy, South Australia and the Netherlands.

The breast cancer mortality reduction in the different case-referent studies ranged from 38% to 70% in the screened versus the unscreened women. Although we found many minor differences in the set up of the six case-referent studies, the overall design

was similar. Inclusion of the first years of screening and the correction factors used for self-selection bias probably explain some of the differences in the magnitude of the effect estimates. However, other factors, e.g. the organisation of the service screening programme, will have an effect on the variation in mortality reductions.

Breast cancer screening effectiveness and the case-referent design: a well matched pair

The results of this thesis show that screening, i.e. early detection and treatment, brought about a substantial reduction of breast cancer mortality in screened versus unscreened women, indicating that the Dutch breast cancer screening programme is highly effective in reducing breast cancer mortality (OR = 0.42, 95% CI 0.33 to 0.53). We have shown that the case-referent study is a valid and feasible tool to monitor the association between breast cancer screening and breast cancer mortality, if comparability between screened and unscreened women is guaranteed. Therefore, it is essential to correct the odds ratio, emerging from the case-referent study, for self-selection bias, if present. We showed that self-selection bias only plays a minor role on the overall effectiveness estimate of breast cancer screening.

The case-referent design can be used for future evaluations if changes and improvements over time related to breast cancer screening are expected to have an influence on breast cancer mortality, like changes in incidence or improvements in treatment. All future case-referent studies should address the application of a correction factor for self-selection. For the Netherlands, no more recent correction factors can be estimated. Future changes might influence the plausibility of the correction factors based on the years 1990-1995. Therefore, an understanding of potential indicators for self-selection bias is essential for the future use of case-referent designs.

For the evaluation of the Dutch breast cancer screening programme now and in the future, breast cancer screening effectiveness and the case-referent design are a well matched pair.

Samenvatting

Op basis van de resultaten van wetenschappelijke studies uit de jaren ’70 en ’80 is besloten om in Nederland het bevolkingsonderzoek naar borstkanker in te voeren. De implementatie hiervan is gestart in 1989 en landelijke dekking werd bereikt in 1996. Nu het programma twintig jaar bestaat willen we weten hoe groot de daling van borstkankersterfte door het landelijk bevolkingsonderzoek naar borstkanker is. Om dit effect te kunnen bepalen is het patiëntcontroleonderzoek een geschikte methode. Bij deze complexe onderzoeksmethode dient men rekening te houden met een aantal methodologische aspecten. In dit proefschrift gaan wij hier uitvoerig op in en onderzoeken wij hoe bruikbaar het patiëntcontroleonderzoek is voor het monitoren en het evalueren van de invloed van het bevolkingsonderzoek naar borstkanker op de borstkankersterfte in Nederland.

Bij het patiëntcontroleonderzoek vergelijken wij de borstkankersterfte in een groep gescreende vrouwen ten opzichte van de borstkankersterfte in een groep niet-gescreende vrouwen. We hebben individuele gegevens over deelname aan het bevolkingsonderzoek gekoppeld aan individuele gegevens over borstkankersterfte. Met deze gegevens hebben we zowel regionaal als nationaal het effect van screening bepaald. Daarnaast hebben we, met behulp van gegevens uit de implementatieperiode van het bevolkingsonderzoek, regionale correctiefactoren uitgerekend om te kunnen corrigeren voor eventuele zelfselectiebias. Zelfselectiebias kan optreden als de groep vrouwen die deelneemt aan het bevolkingsonderzoek een ander basisrisico op borstkankersterfte heeft dan de groep vrouwen die niet deelneemt. Verder hebben we onderzocht of verschillen in de methode van het patiëntcontroleonderzoek kunnen leiden tot de internationale verschillen in gevonden daling in borstkankersterfte. De werking van een bevolkingsonderzoek is ook afhankelijk van de incidentie in een populatie. Daarom hebben we eerst gekeken naar veranderingen in de kans op borstkanker sinds de invoering van het Nederlands bevolkingsonderzoek naar borstkanker.

De kans op borstkanker

Het risico dat een Nederlandse vrouw bij geboorte heeft om gedurende haar leven borstkanker te krijgen kan worden bepaald met behulp van populatiegegevens. De kans om borstkanker (zowel invasief als in situ carcinoom) te krijgen is gestegen van 1 op 10 in 1989 naar 1 op 7 in 2003. De kans om aan borstkanker te overlijden is gedaald van 1 op 22 naar 1 op 26.

Het effect van screening op de sterfte aan borstkanker

In de trials in de jaren ’70 en ’80 is een daling in borstkankersterfte van 25-30% gevonden bij de groep vrouwen die was uitgenodigd voor mammografische screening. Op basis van deze studies zijn er in het begin van de jaren ’90 in veel Westerse landen screeningsprogramma’s ingevoerd. Om de beoogde sterftedaling betrouwbaar te kunnen bepalen is het belangrijk om de doodsoorzaak van een vrouw te koppelen aan haar deelname aan het bevolkingsonderzoek. Bij het patiëntcontroleonderzoek wordt de deelname van aan borstkanker overleden vrouwen vergeleken met de deelname van vrouwen die voor screening zijn uitgenodigd. Dit resulteert in een odds ratio (OR), de uitkomstmaat van het patiëntcontroleonderzoek. De OR hebben we gecorrigeerd voor eventuele zelfselectiebias met regionale correctiefactoren.

Het patiëntcontroleonderzoek uitgevoerd in de provincie Limburg liet een sterftedaling van 70% zien bij de gescreende vrouwen ten opzichte van de niet-gescreende vrouwen (OR = 0.30, 95% CI 0.14-0.63). Na correctie voor zelfselectiebias was de sterftedaling 76% (OR = 0.24, 95% CI 0.24-0.58). In het landelijke patiëntcontroleonderzoek vonden we na correctie voor zelfselectiebias een sterftedaling van 58% (OR = 0.42, 95% CI 0.33-0.53). Uit bovenstaande gegevens blijkt dat het Nederlands bevolkingsonderzoek naar borstkanker effectief is in het verlagen van de borstkankersterfte.

Zelfselectiebias

Een probleem van het patiëntcontroleonderzoek is dat zelfselectiebias mogelijk een rol speelt in de schatting van het effect. Om hiervoor te corrigeren hebben we correctiefactoren berekend met behulp van de *incidence-based mortality* methode. Hierbij wordt een correctiefactor bepaald uit een groep van niet-gescreende en een groep van niet-uitgenodigde vrouwen. Beide groepen hebben we geselecteerd uit de implementatieperiode van het bevolkingsonderzoek, waarin een deel van de vrouwen nog geen uitnodiging had ontvangen.

Voor vijf screeningregio’s in Nederland hebben we correctiefactoren berekend, die onderling van elkaar bleken te verschillen. Dit toont aan dat het noodzakelijk is om per land of regio een correctiefactor voor zelfselectie te bepalen. In drie regio’s leidt correctie voor zelfselectie niet tot een verandering van de OR en in de andere twee regio’s wordt het effect van screening groter, dat wil zeggen een iets grotere sterftereductie. Gelet op alle regionale correctiefactoren is de invloed van zelfselectie in Nederland echter gering.

Verschillen in de methode van het patiëntcontroleonderzoek

Recent uitgevoerde patiëntcontroleonderzoeken naar de effectiviteit van het bevolkingsonderzoek naar borstkanker tonen verschillen in de grootte van de sterftedaling. We hebben gekeken of variaties in de gebruikte studiemethode deze verschillen kunnen verklaren. In deze studie hebben we zes patiëntcontroleonderzoeken meegenomen, uitgevoerd in East Anglia (Verenigd Koninkrijk), Wales, IJsland, Centraal- en Noord-Italië, Zuid-Australië en Zuidoost-Nederland.

De daling in borstkankersterfte in de verschillende patiëntcontroleonderzoeken varieerde van 38% tot 70% in de gescreende versus de niet-gescreende groep. Er waren veel kleine verschillen in de opzet van de zes patiëntcontroleonderzoeken, maar de toegepaste methode was in grote lijnen gelijk. Een deel van het verschil in de grootte van de sterftedalingen wordt mogelijk verklaard door het meenemen van gegevens van de eerste jaren na de start van het bevolkingsonderzoek en de gebruikte correctiefactoren voor zelfselectiebias. Het merendeel van de verschillen zal echter komen door andere factoren, zoals de organisatie van het bevolkingsonderzoek.

Effectbepaling van screening en het patiëntcontroleonderzoek: een prachtig paar

In dit proefschrift hebben wij aangetoond dat screening, dat wil zeggen de combinatie van vroege ontdekking en therapie, leidt tot een substantiële daling in borstkankersterfte voor gescreende vrouwen versus niet-gescreende vrouwen (OR = 0.42, 95% CI 0.33-0.53). Conclusie: het bevolkingsonderzoek naar borstkanker in Nederland werkt. Verder hebben wij laten zien dat het patiëntcontroleonderzoek een betrouwbare en uitvoerbare methode is om het verband tussen screening en borstkankersterfte te monitoren. Hiervoor is het essentieel om de OR te corrigeren voor zelfselectiebias, indien het aanwezig is. De invloed van zelfselectiebias in Nederland is gering.

Bij toekomstige veranderingen die van invloed kunnen zijn op borstkankersterfte, bijvoorbeeld de toename van de incidentie van borstkanker en verbeteringen in de therapie, is het patiëntcontroleonderzoek een goed evaluatiemiddel. Bij alle toekomstige patiëntcontroleonderzoeken moet rekening gehouden worden met zelfselectie. Mogelijk moeten in de toekomst de correctiefactoren voor zelfselectie opnieuw worden bepaald. Het zou kunnen dat de correctiefactoren uit de jaren ’90 tot en met ’95 in de toekomst niet meer bruikbaar zijn, door bijvoorbeeld veranderingen in deelname aan het bevolkingsonderzoek en de redenen hiervan.

Kortom: de evaluatie van het effect van screening op de borstkankersterfte in Nederland en het patiëntcontroleonderzoek zijn een prachtig paar, nu en in de toekomst.

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About the author

Ellen Paap (21-01-1981) was raised in Zandvoort. She completed secondary school in 1999 at Stedelijk Gymnasium in Haarlem. In 2000 she started with the study Health Sciences at Maastricht University. She specialized in Movement Sciences and for her internship she looked at the physiologic response of the six-minute walk test in children with juvenile idiopathic arthritis at the department of Pediatric Physical Therapy & Exercise Physiology, Wilhelmina Children's Hospital. After graduation in 2004 she worked as a research assistant for a project on the influence of a lifestyle intervention programme at the VU Medical Centre. In 2006 she worked as a public health researcher at the GGD HollandsMidden.

From December 2006 till August 2011 she worked on her PhD project at the department of Epidemiology, Biostatistics and HTA of the Radboud University Nijmegen Medical Centre (RUNMC) of which the results are described in this thesis. For her project she spent six weeks at the Clinical and Descriptive Epidemiology Unit, ISPO – Cancer Prevention and Research Institute in Florence, where she worked on the incidence-based mortality method used to correct for self-selection bias. Since September 2011 she is appointed as scientific researcher at the National Expert and Training Centre for Breast Cancer Screening (LRCB).